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FLYING DOCTOR "LOCUM".[1]

By DOUGLAS GALBRAITH,
Melbourne.

THIS is not in any way a scientific paper, but an attempt to tell you briefly something of my personal experiences in a medical service of which Australia is justly proud; and since much of the work was with children there could be something of pædiatric interest.

Last winter I travelled for four months around North Queensland and half of this time was spent as a "locum" in the Royal Flying Doctor Service of Australia, based at Charters Towers.

You may with justice wonder how a pædiatrician, no longer—let us be euphemistic—in the first flush of youth, came to be doing this job. It was entirely due to the persuasion of that great Australian and fine doctor, the late George Simpson who, when told that I was anxious to do some work among the aboriginal children in the Cape York Peninsula, suggested, gently but firmly, that I relieve for two months Ken Pettit at Charters Towers. This idea startled me. I jumped back like a rabid Rechabite being offered a rum cocktail. Terrible visions went through my mind of women in difficult labour, of uncontrollable hæmorrhages and of tough stockmen thrown from wild mustangs and lying helpless with a fractured skull or pelvis or a ruptured liver. It would obviously be completely stupid of me to attempt this work. Yet such was the charm and the strength of George Simpson that in some sort of hypnotic trance I said I would try to do it.

Dr. David Jackson was with me when Dr. Allan Vickers, Medical Superintendent in Queensland of the Royal Flying Doctor Service, told me many lurid stories of his early pioneering experiences as a flying doctor; and David confided to me afterwards that he thought I should at once have "high tailed" it back to Melbourne.

Actually, although I was pretty scared a good deal of the time, luck was with me and nothing desperate happened. I can therefore recommend other pædiatricians to have what I am sure they will find a wonderfully exciting and rewarding experience.

I will not enlarge on the historical background of the Royal Flying Doctor Service. You will all know about

[1] Read at a meeting of the Australian Pædiatric Association on April 22, 1961, at Canberra.

John Flynn, who, in 1911, as Presbyterian minister to Beltana in South Australia, realized the terrible isolation of families in many parts of Australia and their frightening problems in illness, accident and childbirth. Children and adults had died because they could not get medical aid.

Flynn saw that the answer lay in a trinity—a trinity of medicine, aviation and radio; and the hardest of these was radio. The break through came in 1926 when Alfred Traeger, a young South Australian, invented the now famous pedal radio, the simple device of a tiny dynamo charged by a rotating energy which worked by bicycle pedals. And so in 1927 John Flynn and George Simpson made the first medical aerial survey and the first Flying Doctor Base was established in Cloncurry.

There are now 12 bases around Australia. Three of these are in Queensland and their president is Dr. Alan Earnshaw, a former president of the Australian Pædiatric Association.

Now I want to take you to Charters Towers, that old gold-mining town 90 miles inland from Townsville, which was to be my headquarters for two of the most interesting months of my life.

Dr. Ken Pettit, whom I was to relieve, is a very able and energetic young Melbourne graduate. Sitting in the flying doctors' residence at Charters Towers he outlined to me my duties, and on a large wall map showed me my "parish", which was actually a large part of the Cape York Peninsula and covering more than 200,000 square miles. In brief the duties were: (i) to conduct consultations by radio-telephone from Charters Towers; (ii) to fly to emergency cases, usually bringing the patient back to hospital at Charters Towers; (iii) to carry out a regular weekly flying circuit and conduct clinics at various centres on the peninsula, usually at outlying cattle stations or old gold-mining towns, and to visit the mission stations on the Gulf of Carpentaria. He said that the clinics were like general practice consultations and included ante-natal and post-natal work and many inoculations for children.

Dr. Pettit explained to me about the Royal Flying Doctor Service medical chest which is kept at all out-back centres. This chest contains about 60 drugs and medicines and about 30 items of dressings and minor surgical equipment. Each item is numbered and there is a key book, so when the doctor prescribes during a radio consultation he simply gives the number of the preparation he wants used.

Additionally, there is a chart at each centre on which the front of the body is divided into numbered and the back of the body into lettered squares. The person describing the symptoms to the doctor on the radio-telephone can thus indicate the location.

We then went along to the Royal Flying Doctor Service Radio Base, the nerve centre of the Service, to meet Vernon Kerr, the versatile and very skilled radio operator. Here, at 8.30 a.m. each day when in Charters Towers, one conducted the medical radio-telephone session.

I shall pause here in the narrative and say a word about these radio consultations. I found them quite difficult. There is a definite technique to be learned in trying to sum up, on a one-way line, the information given and make a diagnosis with the patient perhaps 200 miles away. One had to make up one's mind whether to fly out to see the patient or whether it was safe to temporize. This part of the work caused me considerable anxiety, although the golden rule was: "When in doubt, go."

One typical example of an unequivocal emergency was a Sunday morning call from a young mother whose child, aged 17 months, had swallowed a considerable quantity of petrol. This was from an isolated district with bad roads and 120 miles away. Within three hours of getting the call we had flown out and treated the child, transported her back and tucked her up in a cot in the Charters Towers Hospital. Flights like this can be truly life-saving.

In these radio-telephone conversations one presses a button on the microphone to talk and finishes that bit of the conversation, perhaps after asking a question, by saying "over". When signing off at the end of the conversation one says "over and out". There is a delightful true story of a small boy at one of the outback cattle stations who was accustomed to these radio-telephone conversations and who, when saying his prayers, would sign off with: "Goodnight, God. Over and out."

Now I must pick up the thread of my narrative again. Ken Pettit and I talked that evening until nearly midnight, and then this energetic young doctor had me out of bed at 4 a.m. next day to be ready for a 6 a.m. take-off. There was a good deal of gear to be taken out to the aircraft. For each flight this includes medicines, drugs, emergency surgical equipment already sterilized, dental forceps, oxygen apparatus, intravenous sets and a small, refrigerated box with vaccines, sera and snake-bite anti-venene, particularly for the taipan.

It was still dark when we got out to the airstrip, where Neil Harris, the pilot, was already warming up the three engines of the De Havilland Drover. After a quick and methodical loading, not forgetting the newspapers and parcels for the outback stations, we were ready. Ken Pettit shook my hand and wished me luck — I did think there was a quizzical look in his eye — and then we were airborne; and I was the flying doctor for the Cape York Peninsula. My mouth got dry even thinking about it. It seemed to me that my family motto must be: "Fools rush in."

The cabin had four seats and one stretcher. Everything, except me, looked efficient and business-like. Still, it was a wonderful sensation to be in the sky with the dawn breaking.

On this first week's schedule the clinics were held at old gold-mining towns or cattle stations. These clinics were to me very interesting, with a wide cross-section of ailments and ages. The clinics were also a social event. People came in from long distances and had a good old gossip on "doctor's day".

At the airstrips the ambulance would sometimes be waiting and often there were consultations there. Typical old, nearly empty, gold-mining townships included Mount Coolum, where the clinic was held in the large hall adjoining the one and only grocer's store *cum* post office. At Ravenswood the clinic was held near the old hotel, which has the shaft of a disused gold mine right at the bar door. In its boom days Ravenswood had quite a good-sized hospital, of which only the walls of the operating theatre remain.

Typical of the cattle stations at which clinics are held is Lyndhurst, the home of Mr. and Mrs. Phil McNamara. Mrs. McNamara writes novels under the pen name of Elizabeth O'Connor and recently won a high literary award for her book "The Irishman", which is about North Queensland. Further north, Wrotham Park is one of the largest cattle stations, with an area of about 4000 square miles.

I secured quite a few aerial photographs from the dropping hatch of the aircraft. To get them I would wedge myself firmly beside the door of the aircraft and pull inwards the dropping hatch. Then the pilot would bank over to give me an unobstructed view. To steady myself at this angle of 45° and not fall out, I would hold on firmly to a small handle just beside the door. After doing this for several weeks I said one day to the pilot: "Neil, what's that little handle with a bit of copper wire on it near the door? What happens when you pull it?" I could see Neil's pupils dilating as he replied: "The whole so-and-so door falls off. That's what happens." After that I left the little handle severely alone.

I now want to take you for a quick journey to the mission stations on the Gulf of Carpentaria. I particularly want to tell you about some of the aboriginal children, of whom I examined about 300, because I am interested

in their type of physique and bone structure. In a clinic at one of our children's hospitals we see children of all physical types—stocky, slender, thick-boned, fine-boned and so forth. This is not so, in my limited experience, with a group of aboriginal children. Practically all—both boys and girls—have long, slender limbs with particularly fine bones, which are in contrast to an abnormally (to us) thick skull bone. The increase in bone length of limbs seems to commence about the fifth year and is most marked in the proximal bones, the humerus and the femur. The feet are universally large, flat and mobile, and almost as efficient as hands. Another interesting point is the small amount of subcutaneous tissue. At first in vein puncture I kept going right through the vein.

I must not start to expound on this, but I wish I knew more about it. Could this physical structure be an adaptation over the centuries to the survival needs of these people? The aboriginal of the Cape York Peninsula has lived by hunting and fishing. He can still cover immense distances through the bush on his big flat feet. He has had to be agile, to travel fast and to develop great muscle coordination; and so maybe he "fined-down" his bones and shed his subcutaneous tissue. As a contrast, in the Torres Strait island children these features are not nearly so marked.

Now we come back to facts and the Gulf of Carpentaria. Our first call was at the Mitchell River Church of England mission station, in its beautiful setting. From here we flew low along the rivers and coastline, sighting crocodiles, dingoes and wild pigs, until we came down at the Edward River Church of England mission, where David Halliday and his wife made us welcome. It is unpleasant to recall that for about five months of the wet season this mission is still cut off from medical help and that deaths have occurred because of this.

Early next morning we flew on to the Presbyterian mission at Arukun, where the Reverend Bill Mackenzie and his wife have laboured devotedly for many years. The timber mill here, worked by the aborigines, shows what can be done by our oldest Australians.

From Arukun I had the good fortune on one visit to go northward by ketch to Weipa and to see the low cliffs of red bauxite on this east coast of the Gulf of Carpentaria.

Weipa Presbyterian mission is actually on the great bauxite deposits being developed by Consolidated Zinc. To the missionary, the dauntless Mr. Jimmy Winn, and his wife falls the great task of trying to assimilate some of our Australian aborigines into fast-growing Australian industry. I was interested to see at Weipa an aboriginal girl, Rebecca, aged 12 years, on whose cleft palate Sir Kenneth Fraser operated when she was two years old. The result is very good.

The mission station furthest north on the Gulf is the Presbyterian mission of Mapoon. This was the earliest of the missions and its surroundings are truly tropical.

These mission stations are doing wonderful work and the good nutrition of the aboriginal children in their care is noteworthy.

Finally, I was able to go later on to Thursday Island and from there by ketch to the island of Moa, where there is, at St. Paul's, a Church of England mission and a theological college. Time does not permit to talk of these very interesting Torres Strait islands. They are certainly worth a visit.

In conclusion, I want to say how proud I am that I have had the opportunity to serve, even for a short time, in this Royal Flying Doctor Service of Australia.

This service has indeed spread a mantle of safety over many Australian families in lonely places. In this service our young Australian doctors have built up an outstanding reputation for efficiency, kindness and comradeship; so that for any member of our profession who goes to this northernmost part of Australia there is the hand of welcome outstretched and the friendly door wide open.

THE DIAGNOSIS OF MENTAL RETARDATION.[1]

By F. Grunseit, M.B., B.S.,
Sydney.

The recognition of mental retardation as a medico-social problem is of comparatively recent origin. A new interest in this subject was very much in evidence during 1960, when there were held in London a Conference on the Scientific Study of Mental Deficiency and the First International Conference on Congenital Anomalies, while in Edinburgh a Conference of the World Federation for Mental Health took place. A number of basic changes are taking place in our thinking about this subject and these have altered the approach to diagnosis, to treatment and to research into mental deficiency.

Because most pædiatricians have felt that mental retardation is the province of the social worker, the educator and the psychiatrist, only a few have recognized the total care of retarded children as part of their work. The magnitude of the problem is often not recognized, or is simply denied (Masland, 1958).

It is estimated that in the United States of America there are 5 million retarded individuals, of whom 1·5 million are children. Every year 120,000 new-born infants are mentally retarded. Since the survival rate of these individuals is increasing, a rise in these figures may be expected (Masland, 1958).

Mental retardation has been defined as that condition of mental maldevelopment, arrested development, deficiency or deterioration which exists from an early age. This state always affects intelligence, judgement and the capacity for adjustment and economic efficiency. This definition implies a permanence which leaves little hope for improvement. Only about 5% of patients are amenable to medical treatment.

The purpose of painstaking diagnosis has therefore been questioned, if in the end nothing can be achieved; but mental defect is nothing more than a symptom. Because this has not been thoroughly recognized, little progress has been made in the field.

The ætiological factors acting in the prenatal period are thought to be responsible for most of the cases of severe and moderate retardation in which institutional care is required. The detailed study of the more severe forms of mental defect may provide us with information useful in the minor forms of defect. Prenatal factors include hereditary ones, which may produce familial or genetically determined disease, such as inborn errors of metabolism, disorders associated with maldevelopment of the skull (some cases of microcephaly and craniostenosis) and congenital "neuro-ectodermoses". Other prenatal factors are prenatal infections, congenital hypothyroidism, prenatal pelvic irradiation (this has been queried) and mongolism. Perinatal factors include trauma, hypoxia, hæmorrhage, prematurity, post-maturity and kernicterus. Post-natal factors include central nervous system infection, cerebral trauma, hæmorrhage (intracerebral, subdural or subarachnoid), exposure to toxic agents (such as lead encephalopathy) and functional pseudo-retardation.

Some of the detailed knowledge about the rare inborn errors of metabolism came after a large number of individuals were examined and investigated. One of the methods used for this purpose was urinary chromatography. With its aid, the presence or absence of certain diseases can now be determined, and we can give advice to families in which the question of inborn disease may arise.

The frequency of the genetic factor in mental retardation has become apparent through the study of congenital anomalies. The total incidence of inherited conditions

[1] Read at a meeting of the Australian Pædiatric Association on April 22, 1961, at Canberra.

due to genetic causes, excluding mongolism, was about 5% in one large institution.

The inherited biochemical abnormalities associated with mental retardation would seem in many instances to be transmitted by autosomal recessive genes. Approximately one person in 70 carries the gene responsible for phenylketonuria, and the incidence of other genetically determined abnormalities in the population may be high (Roberts, 1959).

The detection of abnormal variants in the population and the identification of carriers of traits has been made possible in some instances by the development of mass screening techniques. Loading doses of substances can be given in order to identify biochemical pathways. Phenylalanine tolerance curves, for instance, can be used to identify heterozygote carriers of the gene for phenylketonuria in families affected by the disease (Falls and Neel, 1954; Hsia, 1960).

The gene does not act singly and in an isolated way, nor is its action subject to an all-or-none law. The environment and all other genes are able to influence gene action, so that a very complex picture results. Hence different degrees of penetrance are observed and these may produce all the changes, from a fully expressed disease to a mere susceptibility in some individuals. Sometimes, as in tuberous sclerosis, only the merest skin defect may be evidence of the presence of abnormal genes (Fraser, 1959).

Mental retardation is fairly common in individuals showing chromosomal anomalies involving abnormal numbers of autosomes or sex chromosomes and structural changes. In mongolism one finds often that there is trisomy of the small acrocentric chromosome owing to non-disjunction during meiosis. In a few cases of mongolism, reciprocal translocation of the small acrocentric chromosome onto a larger chromosome is found, the apparent number of chromosomes being 46. This translocation may also be transmitted by either parent whose chromosomal complement is 45. The child, although apparently normal, may in turn produce a mongoloid offspring. It follows that all mongoloids should be submitted to chromosomal analysis, since in some instances prevention of mongolism is possible. It also follows that variations of these syndromes and other as yet unidentified anomalies of chromosomes will be detected if the chromosomes of individuals with probable defects are analysed (Turpin, 1960; Warkany, 1960).

The frequency of sex chromosome anomalies in male defectives is somewhere between 1% and 3%. Intellectual subnormality occurs in 25% or more of chromatin-negative patients with webbing of the neck and other evidence of gonadal dysgenesis. It is also stated that 20% of defective females suffer from primary amenorrhœa. The incidence of Klinefelter's syndrome is probably about one in 500 males, but this syndrome occurs 10 times more frequently in intellectually handicapped males.

The essential step, then, in all these studies, is the identification of the affected individual. The next step is the realization that information regarding some well-known syndromes, such as mongolism or phenylketonuria, is as yet incomplete and that a great deal of further experiment and observation is necessary. Warkany states that the discovery of the extra chromosome may merely have added yet another theory to the 39 which exist of causes of mongolism, but that it will bring new interest to the study of this syndrome (Warkany, 1960).

The effects of asphyxia on primates are being studied in a monkey colony in Puerto Rico under the auspices of the National Institute of Neurological Diseases and Blindness. By separating the placenta and artificially resuscitating the baby Rhesus, syndromes closely resembling brain damage and mental retardation in the human have been produced. In addition, one may mention the 10-year cooperative study of 40,000 births with regard to maternal influences, bleeding in pregnancy, prematurity and brain damage. This project is being carried out by 15 major hospitals in the United States at a cost of 10 million dollars. It is often said that research in this field is costly in relation to results. However, as the estimated cost of maintaining one defective child in an institution for many years may amount to 100,000 dollars, prevention of mental defect, even in individuals, is economically justifiable (Aldrich, 1960).

One of the first approaches to the study of prevention of mental deficiency should be the provision of complete diagnostic services in the form of special clinics along the lines of those begun during the last 10 years in the United States of America, where these services are available to all, regardless of financial status (Wortis, 1954).

It is sometimes argued that the provision of such separate centres is a form of unnecessary specialization, and that retarded children are best dealt with by existing out-patient facilities, school medical services, as in England, or private practice. However, experience has shown that this is not so. For the first time, a dual purpose has been achieved by these clinics — namely, accurate assessment of the patients and authoritative, sympathetic counselling of the parents (Kanner, 1956). There are now over 70 such centres in the United States of America. While I was working in Cincinnati recently it soon became obvious to me that the clinic there was providing such an effective service.

From the point of view of the parents, the interviews with several workers had a therapeutic effect in themselves. From the point of view of the staff, the constant cooperation of all members provided a very critical approach to each problem and ensured that an unbiased and many-sided view was taken. Again, from the point of view of clarity of interpretation, the individual members of the clinic did not discuss their own views with the parents, but their collective findings were presented to the parents by the director of the clinic during a final interview. It is a difficult matter for the parents to understand and to accept all the facts presented to them, and it has therefore been found extremely useful to invite them to further interviews (Jensen, 1960).

The matter of counselling had previously been much neglected, because it was wrongly concluded that once the term "mental deficient" had been applied to a child, the only positive advice which could be given was that of institutional placement. The severe emotional disturbance existing in a family with a retarded child was thus greatly aggravated and the parents were left with their feelings of hopelessness, shame, guilt and frustration. This situation often resulted in mistrust and actual hostility towards the medical profession.

Medical teaching of this subject in most schools has to date been very elementary, and often merely tended to perpetuate the prejudices and erroneous concepts of a bygone age.

Why is it that an emotionally disturbed child, a child with learning problems or even a child with an early psychosis whose intelligence quotient may be well above average, is considered a worthy recipient of all the aids at our disposal at the earliest possible moment? It is because if treatment is effective, there is restored to the community a socially acceptable individual. In the case of the retarded child, this help is often withheld in the belief that he is less deserving, since his intellectual handicap is permanent. Here lies the fallacy, for our aid must be impartial. It is the right of every child to receive whatever help is necessary so that he may reach his optimal development, as it is the right of all parents to be helped with their problems.

The United Nations has recognized the needs of the mentally handicapped child and has incorporated this principle in its "Declaration of the Rights of the Child". Principle V reads: "The child who is physically, mentally or socially handicapped shall be given the special treatment, education and care required by his particular condition."

It is an accepted fact that every child needs adequate stimulation during early life. Unless such stimulation

is forthcoming at the appropriate time, physical and emotional development is defective (Gesell, 1947, 1948). The provision at an early age of good training facilities for children selected by proper diagnosis has resulted in development to a standard higher than expected. As these children grow up, they can be gainfully employed in workshops or in industry instead of being a complete burden. When one is certain—but only when one is certain—that significant retardation is present, one should inform the parents. Failure to do so leads to the continuation of false hopes and tends to place the child in a situation with which he is unable to cope. In this way, emotional disturbance is added to his existing handicap and leads to a much more complex state of affairs.

On the one hand we are presented with facts suggesting that brain injury is extremely common and that it starts with very minor defects of brain function barely detectable and often attributed to vague genetic or environmental causes. On the other hand, we are told that cerebral damage, when present, is obvious enough and can be diagnosed without much doubt. Improvement may occur quite remarkably in the first few months, thus suggesting the need for great caution in giving a prognosis at a very early stage (Masland, 1958; Illingworth, 1960).

Children with brain damage require a great deal of support and the building up of emotional security must commence at the earliest age. Although the high incidence of mental defect in children with cerebral palsy is well known, this fact has been glossed over by some of the organizations caring for them, thus denying these children the benefit of therapy because their intelligence quotient does not reach an arbitrary standard (Patterson, 1958)

Another special problem is presented by the child with impaired development of receptive or expressive language. The differentiation of these disorders from mental retardation is not easily made, but in general, the retarded child is different in degree, and his performance is impaired equally in all fields. The child with language problems is different in kind, and his performance varies a great deal, being above normal in some respects and below average in others. Special training must be begun as early as possible, certainly by the age of three years. This seems to have been accomplished in a satisfactory manner by kindergartens attached to speech and hearing clinics (Wood, 1960).

The early recognition of childhood schizophrenia and autism, and their distinction from other causes of retardation, present another diagnostic problem. Much work has been done with these children, yet the number admitted to institutions has not decreased, thus demonstrating the need for further research.

Finally, there are those children suspected of mental defect whose problem is mainly one of emotional disturbance. They may show marked opposition to learning, and general behaviour may be inconsistent with their age. If in addition speech development is delayed, or if other deviations from standard performance are found on testing by a psychologist, the findings may be wrongly interpreted as showing mental defect. It is an interesting phenomenon that we only relate abnormal behaviour to the intelligence quotient when it is below normal (Illingworth, 1959).

In this outline of a complex subject an attempt has been made to show what is being done and what still needs to be accomplished. This is work well worthy of the efforts of pædiatricians who are naturally interested in the medical, social and emotional aspects, as well as in the purely scientific side of child care.

In April, 1846, Dr. Samuel Gridley Howe of Boston became interested in conducting a survey of "human beings condemned to hopeless idiocy". During the following two years he visited 63 towns and examined 574 individuals. His report closed with these words:

> There is not one of any age who may not be made more of a man and less of a brute by patience and kindness directed by energy and skill.

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UNUSUAL CAUSES OF STEATORRHŒA IN INFANCY AND CHILDHOOD.[1]

By CHARLOTTE M. ANDERSON, M.D., M.Sc., R. R. W. TOWNLEY, M.R.A.C.P., MAVIS FREEMAN, M.Sc., AND PATRICIA JOHANSEN, M.Sc.,

Clinical Research Unit, Royal Children's Hospital, Melbourne, Victoria.

IN a community of predominantly European origin the great majority of babies and young children with persistent steatorrhœa or malabsorption of fat from the small intestine, associated with failure to thrive, suffer from either cœliac disease (wheat gluten intolerance) or fibrocystic disease of the pancreas. A few have persistent small intestinal infection, bacterial or parasitic (from, for instance, the salmonella organisms or *Giardia lamblia* infestation). However, there are some patients whose steatorrhœa is of other origin. The ætiology of the steatorrhœa in these patients is very varied and sometimes difficult to elucidate. In the following discussion a complete classification of the causes of steatorrhœa or malabsorption from the small intestine is not intended, but the experience of one group of workers during the investigation of a series of cases will be described. Other investigators have and will undoubtedly come across additional unusual causes of steatorrhœa.

The primary function of the small intestine is that of digestion and absorption of foodstuffs. Any abnormality in its complex physiological functioning may result in maldigestion and malabsorption. The small intestine has immense reserves, but must fulfil certain criteria in order

[1] Read at a meeting of the Australian Pædiatric Association on April 22, 1961, at Canberra.

to carry out its function adequately: it must be of sufficient length and capable of undisturbed forward propulsive movement of its contents; it must receive certain digestive juices in adequate quantities from more distant organs; and it must possess a mucosal lining capable of the complex mechanism of absorption of digested food products, as well as resynthesis and transportation of these substances into the blood-stream and lymph vessels. Detailed knowledge of the multitudinous enzymatic and chemical processes concerned in this mucosal activity is still far from complete, but it is increasing more rapidly than ever before, owing in large part to the development of many new investigational techniques, including the use of radioactive tracer substances, the ramifications of chromatography and electrophoresis for the identification of chemical substances in mixtures, as well as the availability of living human material obtained by peroral biopsy instruments.

During investigation of a patient with steatorrhœa the physiological mechanisms concerned in digestion and absorption should be kept in mind, and each case should be approached from this viewpoint, first in the consideration of the clinical history and examination, then in the use of the simpler preliminary investigations, followed if necessary by the newer and more complex investigations now available.

Clinical Material.

During the past eight years 266 of the patients referred to this unit for investigation of failure to thrive associated with gastro-intestinal symptoms have been proven biochemically to have steatorrhœa. By steatorrhœa is meant the passage of excess fat in the stools—that is, over 4 grammes per day during a period of from three to eight days. This is accepted as meaning malabsorption of fat, and is commonly used as an index of general malabsorption in the small intestine. Balance experiments designed to test the total absorption of protein and carbohydrate are difficult and their results are often misleading; except in rare instances, they have not been performed in this study. Here the word steatorrhœa is at times used synonymously with general malabsorption in the full knowledge that this is only an assumption.

The 266 patients were divided, after investigation, into three groups. Ninety-three suffered from cœliac disease, 139 from fibrocystic disease of the pancreas, and only 34 from steatorrhœa of other ætiology. That is, 232 or 87% suffered from either cœliac disease or fibrocystic disease of the pancreas and 13% from steatorrhœa of other kinds. It may be explained at this stage that the predominance of fibrocystic disease of the pancreas over cœliac disease would be greatly increased if all patients with the former disease treated at the hospital during the time of the investigation were included; this was not the case, since many patients either died before investigation by us or were not referred, whereas all patients with cœliac disease were referred during this time.

Of the 34 patients with steatorrhœa of "other" ætiology, 13 were found to be suffering from steatorrhœa associated with chronic infections; eight of these infections were located in the bowel and five in the chest. Five patients had deficient pancreatic secretion (distinct from fibrocystic disease); two of the five had diabetes mellitus, two did not, and the deficiency in the fifth case was temporary only. Anatomical alterations accounted for eight cases; five of these eight patients had had an intestinal resection; one had duodenal dilatation; one had scarring of the small intestine; and one had malrotation of the gut. Abnormal mucosa accounted for three cases; one patient suffered from subacute jejunitis; one had a defect of fat transport in the mucosa; and one suffered from acrodermatitis enteropathica.

Cœliac Disease and Fibrocystic Disease of the Pancreas.

The clinical aspects of the two diseases (cœliac disease and fibrocystic disease of the pancreas) are now familiar, and most of these children can be readily recognized as victims of one or the other; only confirmatory tests are needed to substantiate the diagnosis and ensure the relevant treatment. For instance, the cœliac child does well till after the introduction of solid food, then gradually fails to gain weight normally; his appetite decreases, misery, apathy and hypotonia appear, the abdomen becomes distended and the stools become paler, often looser and more frequent, although the last-mentioned feature is variable. Steatorrhœa is then demonstrated by the estimation of fat excreted in the stools during a period of days. Recently peroral small-intestine biopsy has enabled the diagnosis of cœliac disease to be more precisely defined and demonstrates the disease to be one in which the mucosal surface of the bowel is damaged. The symptoms and signs disappear after the removal of wheat and rye gluten from the diet.

The child with fibrocystic disease, on the other hand, fails to grow normally from birth, passes oily, rancid-smelling stools, not necessarily in greater numbers, frequently has a persistent cough or subacute chest symptoms of a bronchitic nature with an obstructive element, and often has siblings similarly affected. On investigation the patient shows large numbers of fat globules in the stool, in contradistinction to the "cœliac" child, who usually does not, and a salty sweat. These two diseases should now rarely be mistaken for each other, fibrocystic disease of the pancreas being diagnosed, in the majority of cases, earlier in life than cœliac disease.

Other Causes of Steatorrhœa.

In some of the heterogeneous group of 34 patients with steatorrhœa of other ætiology, the precise underlying pathology or reason for malabsorption has been difficult to define, but with the physiology of the small intestine in mind, the results of a range of investigations of small-intestinal function have allowed some interpretation, or at least a hypothesis, to be put forward.

Chronic Infection.

Among the patients with steatorrhœa associated with chronic infections, bowel infections included salmonella infection and *Giardia lamblia* infestation. The latter have been described in detail elsewhere (Court and Anderson, 1959).

In none of these children were the clinical symptoms and signs of steatorrhœa and failure to thrive of great severity, and on eradication of the infections they cleared readily. The children with subacute or chronic chest disorders of non-fibrocystic origin were all young—that is, under about 18 months. Their type of steatorrhœa was not due to pancreatic deficiency, and if looked for it would probably be found more frequently in such children. It is usually of secondary importance in the whole clinical picture of the child and the reason for its presence is not clearly defined. It seems to disappear as the chest improves or as the child grows older.

Deficient Pancreatic Secretion.

Of the group of five patients suffering from deficient pancreatic secretion, four were referred as suspected cases of fibrocystic disease of the pancreas, since they had failed to thrive from birth, had abdominal distension and passed large, offensive stools containing fat globules. Two of them were sisters. Pancreatic enzymes were completely absent from the duodenal aspirate in each case. However, the sweat test in all cases produced negative results on two occasions, and at a later stage still does so. At the time of presentation chest infection was not a feature of the clinical history in any of them, and although the sisters have since had frequent upper respiratory tract infections, they have never developed the characteristic pattern of chest illness seen in fibrocystic disease of the pancreas. These sisters have been observed for five and four years respectively and are growing well, with the addition of pancreatin extracts to their meals.

In one of the other patients (a boy, who was first examined at the age of three months) the pancreatic

achylia was temporary. Having progressed well with pancreatic extracts added to meals, at the age of two years he was retested after the cessation of pancreatin administration. Pancreatic enzymes were then present in the duodenal aspirate and the stools were normal. The explanation of this temporary pancreatic achylia is not clear.

The remaining two girls have both pancreatic achylia and diabetes mellitus. The first was found to have pancreatic achylia at the age of six years, although symptoms had obviously been present since birth. Sixteen months later she was found to be suffering from diabetes mellitus as well, and this had probably been present in a mild state for some time before diagnosis. The child has not been maintained on pancreatin, as she has shown an acute reaction, with diarrhœa and vomiting, when given even a single dose of several preparations. This is a reaction we have not otherwise encountered with pancreatic extracts. The other girl was diagnosed as suffering from diabetes mellitus at the age of seven years, but it was not until four years later that the story of her passing large, smelly stools all her life was investigated. The stools contained numerous fat globules and a large quantity of total fat (49 grammes per day), and there were no pancreatic enzymes in the duodenal aspirate. The sweat test gave a negative result, and the chest has always been clear. The child was well grown, weighing 32·9 kg. at the age of 11 years (50 percentile).

Thus there is a small group of children whose pancreatic disorder, leading to deficient exocrine secretion, and in two cases to deficient endocrine secretion, cannot be explained on the basis of fibrocystic disease of the pancreas. Of the four children with seemingly permanent pancreatic achylia, two have diabetes mellitus also. In our experience this has not been seen in over 100 proven cases of fibrocystic disease of the pancreas. There does not seem to be at present any other way, during life, of determining the pancreatic disorder in these cases. All the patients probably have had symptoms since birth and therefore the lesion is likely to be a congenital one. Bodian (1953), in his monograph on fibrocystic disease of the pancreas, reviews the literature describing other diseases of the pancreas in children. Some of the references quoted by him refer to pathological descriptions of the pancreas, but others are clinical. The latter are not fully reliable, as all the cases were described prior to the observation of abnormally salty sweat in fibrocystic disease. Consequently, owing to the great clinical variation seen in patients with this disease, one cannot be certain that it has been excluded. However, two pathological entities are described — namely, congenital hypoplasia of the exocrine pancreas and congenital cystosis of the pancreas. Apparently both of these disorders may produce abnormal exocrine and endocrine secretion. In the first the pancreas is largely replaced by lipomatous tissue. Dr. A. Williams, pathologist to the Royal Children's Hospital, Melbourne, has seen one such case amongst his autopsy material.

Anatomical Alterations.

Five of the group of eight children with anatomical alterations had had extensive resection of the small intestine, four during the neonatal period. Steatorrhœa was associated with diminished length of the small intestine, but also in two cases with disturbed motility at the anastomotic site. These two, and two of the other cases, show how malabsorption may develop when normal peristalsis is upset and there is stasis of intestinal contents, with possibly a proliferation of bacterial flora of the colonic type in the small intestine. In this respect they may be likened to the so-called "blind loop syndromes" seen in adult patients. The remaining child in this group of anatomical alterations is an example of how, on occasions, malrotation of the gut may present with symptoms and signs resembling some features of cœliac disease. This has been well recognized in the literature for many years, but the pathological reason for malabsorption is not always apparent. It has been suggested that damage to the blood supply of the gut may occur during episodes of volvulus, with resulting damage to the absorbing capacity of some parts of the small intestine.

The following are brief case reports of three of these children.

CASE I.—This was a case of duodenal dilatation. The patient, a girl aged three years, vomited intermittently from birth. The vomitus was copious, forcefully ejected and bile-stained. She had only one stool per day, but it was usually of a very pale colour. She weighed 12 kg. — that is, below the 10 percentile for her age. Her previous history revealed that she had had an operation for duodenal stenosis in the early months of life and a duodeno-jejunal anastomosis had been performed. At that time the duodenum was noted to be dilated. Investigation at the age of three years showed that the stools contained up to 23 grammes of fat per day, and that the duodenum was still grossly dilated, extending as a sac across the upper part of the abdomen (Figure I), and

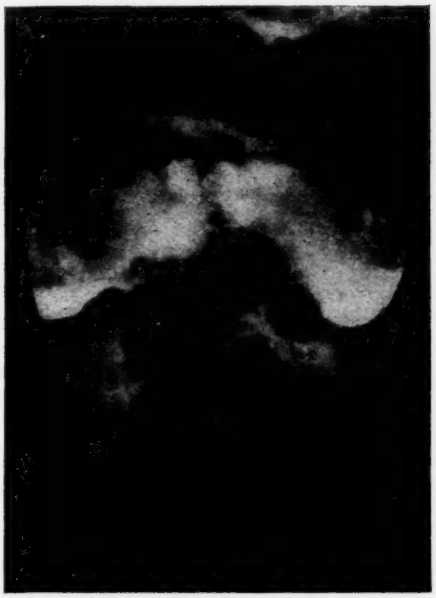

FIGURE I.

Case I. Duodenal dilatation. Röntgenogram showing barium in dilated duodenum with fluid levels.

containing stagnant fluid which on culture produced a profuse growth of bacterial flora of a fæcal type. Subsequently resection of the greater portion of the sac and gastro-jejunostomy were performed. Vomiting ceased, growth has improved and stools have become normal.

CASE II.—This was a case of diffuse scarring of the small intestine. The patient, a boy aged six months, had failed to thrive since birth. He was emaciated, weighing 4·4 kg., had a distended abdomen and passed frequent loose, pale stools. There were no symptoms or signs of respiratory infection. Peristalsis was visible through the thin abdominal wall. The stools were of a thin, porridgy consistency, containing an average of 8 grammes of fat per day when he was having a low intake of fat. Vomiting was minimal. The baby had never been given anything but milk feeds, so that cœliac disease was not considered possible. The lack of respiratory infection in the presence of such gross emaciation is unusual in fibrocystic disease of the pancreas, and as the stools did not contain fat globules and the sweat test gave a negative result, this diagnosis was discarded. Pancreatic enzymes were normal, but a profuse fæcal type of bacterial flora was present in the small intestine. The visible peristalsis had made subacute obstruction seem likely, and a plain X-ray film of the abdomen had revealed fluid levels (Figure II), but a barium follow-through X-ray examination showed

only grossly-dilated small intestine, with no obviously narrowed area. It is well known that radiographic studies of the small intestine with opaque media may be difficult to interpret and narrowing may not be seen. Therefore laparotomy was performed. No single point of obstruction was found, but there were patches of white scar tissue visible on the peritoneal surface of the whole extent of the small intestine. Biopsy of one of these scar patches revealed fibrous tissue replacing both circular and longitudinal muscle layers. This scarring resulted in a gross disorganization of peristalsis in the small bowel, with dilatation and stasis of its contents. The baby subsequently died of inanition and at autopsy the pathologist thought there was also evidence of intrauterine peritonitis.

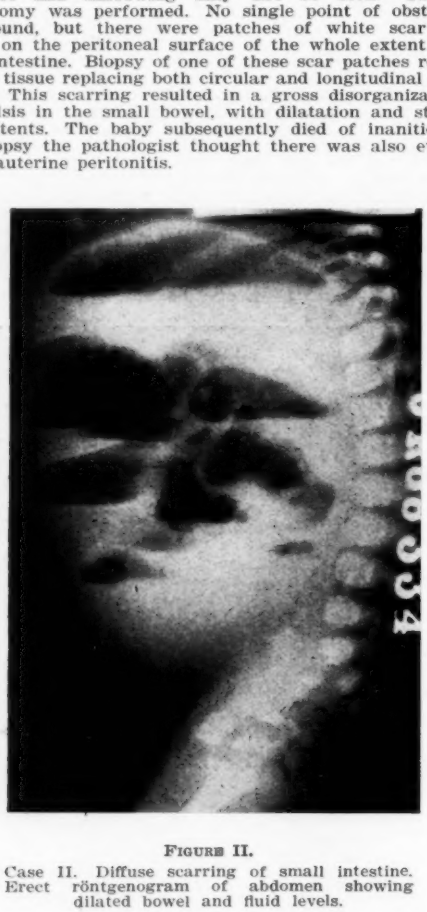

FIGURE II.

Case II. Diffuse scarring of small intestine. Erect röntgenogram of abdomen showing dilated bowel and fluid levels.

CASE III.—This was a case of malrotation with a universal mesentery. The patient, a girl, was first encountered at the hospital at the age of 17 months, with an acute watery diarrhœa of 48 hours' duration, needing intravenous resuscitation. A diagnosis of gastro-enteritis was made, but no pathogenic organisms were found in the stools. However, after three similar attacks during the next 10 months, all of which necessitated her receiving intravenous resuscitation, she was referred for investigation as a possible case of cœliac disease. Several clinical features were against this—notably her good health between attacks, her happy disposition and her good appetite, but her stools were always abnormal, containing up to 14 grammes of fat per day. The abdomen was somewhat distended, and when it was shaken a fluid rattle could be heard. During an acute attack a plain X-ray film of the abdomen showed fluid levels, but it did not do so in between attacks. Barium follow-through X-ray studies at this stage showed that the caecum was on the right side, rather high, but the duodenal loop was not well seen. In the large intestine, instead of being concentrated, the barium became diluted as by a large volume of fluid. The stools did not alter when gluten was removed from the diet and after several months another acute attack occurred. A barium follow-through X-ray study on this occasion showed the duodenal loop to be abnormally situated, and the caecum was shown, in two subsequent films, to occupy a position on the right and then the left side of the abdomen (Figure III). A diagnosis of malrotation was made, and at laparotomy a universal mesentery was demonstrated, it being possible to deliver the whole intestine, small and large, on to the surface of the abdomen. Bands crossing the duodenum were divided. At the time of operation the large and small intestine were somewhat œdematous and thickened. Since that time, seven years age, the child has progressed well with normal growth, but has had, approximately every two years, an attack of acute diarrhœa and dehydration requiring intravenous therapy. Malabsorption is still present, and the stools are soft and large and contain excess fat, but this does not seem to have affected the child's growth. The explanation for the persistent steatorrhœa in this patient is not clear, but there may have been vascular damage in the mesenteries. Recent jejunal biopsy did not reveal any abnormality in the portion of the mucosa that was obtained.

FIGURE III.

Case III. Malrotation with universal mesentery. Röntgenogram with barium in small and large intestine, showing the caecum in different positions in subsequent films.

Abnormal Intestinal Mucosa.

Malabsorption in cœliac disease or wheat gluten intolerance has been shown by biopsy examination of the intestinal mucosa to be associated with mucosal and villous damage, and as the mucosa recovers and the villi reappear after the removal of gluten from the diet, so malabsorption disappears (Anderson, 1960). How wheat gluten initiates the mucosal damage has not yet been explained. Abnormalities in histological structure of the villi have also been described in certain other conditions with malabsorption in adult life—for example, Whipple's disease, tropical sprue and post-gastrectomy steatorrhœa. However, in children, in only rare cases other than "cœliacs" has steatorrhœa been demonstrated to be associated with histological mucosal abnormalities. In two of the following patients a mucosal abnormality has been demonstrated. In the third it has not, but it seems likely that there is at least a biochemical abnormality of mucosal surfaces.

CASE IV.—This was a case of subacute jejunitis. This diagnosis is postulated as that which fits best both the findings and the subsequent progress of a baby girl, who was the youngest of 11 children in a Dutch migrant family living in crowded and poor economic circumstances. The baby was said to be well until she was four months of age, when, on the day educational diet was started, the child commenced to vomit. Three days later diarrhœa commenced, blood and mucus being passed in the stools. She was admitted to the Infectious Diseases Hospital, where adenovirus type 2 was isolated from the stools. During one month in hospital her weight was stationary and she was transferred for investigation. She was an emaciated baby with a distended abdomen, passing pale, porridgy stools, containing an average of 12 grammes of fat per day. There were no clinical signs of chest infection, and in view of her great emaciation it seemed unlikely that fibrocystic disease of the pancreas was the explanation. Babies with this disease who escape chest infection will thrive moderately well. Cœliac disease did not seem a possible diagnosis, as the baby had had no gluten even in her few days of educational diet. No virus or pathogenic organisms were discovered in the stools at this stage, the sweat test produced a negative result, pancreatic enzymes were normal and a barium follow-through X-ray study revealed only a uniform slight dilatation of the small intestine. As at this time the technique of small-intestinal mucosal biopsy had been introduced, a

piece of upper jejunal mucosa was obtained, and Figures IV and V show the appearance under low-power and high-power microscopy. The villi were rather broader than normal, resembling some of the milder degrees of villous change seen in cœliac disease, but the main feature was an increase in inflammatory cells in the lamina propria, many of which were polymorphonuclear cells. During these investigations another month had passed and the child's condition was unchanged; the stools were still frequent, despite an adequate caloric intake of a fat-free milk feeding. It was difficult to keep up fluid requirements, owing to losses in the stools. An attempt was made to investigate the bacterial flora of the small intestine, but duodenal content only was obtained and this was sterile. However, in view of the possibility of an abnormal flora at a lewer level and the presence of polymorphonuclear cells in the biopsy specimen, a course of orally administered antibiotics was instituted. Four antibiotics of varying type were chosen and these were given in small dosage at six-hourly intervals for four days, one at a time. After 16 days the course was recommenced. The baby immediately began to gain weight, increasing from 4·1 kg. to 5 kg. in four weeks. The administration of antibiotics was then ceased for three weeks and the weight was stationary at 5 kg. The régime was recommenced and the baby's weight increased from 5 to 6 kg. in two months. The child was discharged and antibiotics were continued for a further two months at home with good progress. Then antibiotics were ceased, and a normal, instead of fat-free, diet was instituted. Fat excretion in the stools was found to be normal and the mucosal biopsy, when repeated, showed that the polymorphonuclear infiltration had disappeared, although the villi were still a little broader at their tips. Good clinical progress has continued. The ætiological agent producing jejunal inflammation in this case is unknown, although there may be some relationship with the initial viral infection.

CASE V.—This was a case of a defect in fat transport in the intestinal mucosa. This female child of Lebanese parents, who was first seen at the age of seven months, had had persistent diarrhœa and had failed to thrive since birth. The stools were pale, watery and often very numerous. She vomited occasionally and at times became very listless. She had been fed on milk only, but a variety of milks had been tried, including human, cow and goat, with no beneficial effect. There had not been any episodes of chest infection. The parents had two other normal children, were well themselves and were not related, having both been born in Lebanon and having migrated to Australia several years ago. The patient had a grossly distended abdomen and a wasted body, weighing 5·5 kg. The stools did not contain any pathogenic organisms, ova or cysts, but fat excretion was grossly abnormal, there being 10 to 12 grammes of fat per day in the stools on the comparatively low intake of 20 to 25 grammes per day. During most of her stay in hospital the child had to be maintained on a fat-free milk mixture, as a normal feeding would result in copious fluid stools with dehydration. In fact, on several occasions, the fluid loss in the stools was so extensive as to result in great prostration and near death. Gradually all investigations relevant to the elicitation of the cause of the steatorrhœa were carried out and the only abnormal result, as far as the small intestine was concerned, was that of the mucosal biopsy. This was first taken during a laparotomy which was carried out to exclude finally any anatomical abnormality. The mucosal surface of the small intestine on macroscopic examination showed a white stippling like hoar frosting. Hæmatoxylin-eosin stained sections showed an unusual appearance (Figures VI and VII). The pattern in no way resembled that seen in cœliac disease. Villi were present in normal numbers and length and the lamina propria contained the usual pattern of plasma and other cell types. However, most of the villi seemed a little expanded at the tips and for one to two thirds of their distal length were lined by expanded, empty-looking columnar cells with basal, flattened nuclei. A subsequent peroral biopsy taken from the upper part of the jejunum showed the same appearance with hæmatoxylin-eosin stain. A frozen section stained for fat showed that these seemingly large, empty columnar cells were filled with fat, staining red with oil Red O. No fat was observed in the lacteals of the lamina propria. After this a chylomicron count after a fat meal was carried out, but there was practically no increase in particles in the blood during five hours. The serum was noted to be pale and the total lipid content was low (200 mg. per 100 ml.). The child's hydration was extremely difficult to maintain during her stay in hospital and the serum electrolyte levels varied considerably from time to time. Renal function tests did not reveal any abnormality, and at this stage X-ray films of the bones were normal. There was some iron-deficiency anæmia, and this responded to "Imferon", but not to orally administered iron. No further investigations were undertaken then, and the child was discharged from hospital on a low-fat feeding with the normal addition of vitamins. Her progress was fair until she was aged 2 years and 2 months.

At this time Salt *et alii* (1960) published the details of a very similar case, in which the mucosal biopsy findings appeared identical with those described in Case V. The clinical picture was also very similar. However, they had observed abnormal red cells known as acanthocytes in the blood film, and this caused them to liken their case to cases reported by others in which these cells had also been observed together with symptoms of malabsorption. Salt *et alii* extensively investigated the lipid content of their patient's serum and demonstrated that, as well as a very low chylomicron count and total lipid and cholesterol levels, the β-lipoprotein fraction was completely absent. They also demonstrated changes in the β-lipoprotein fraction of the serum of some of the relatives of the child, then postulating that the patient represented a syndrome of genetic origin, comprising a-β-lipoproteinæmia, acanthocytosis and steatorrhœa.

Stimulated by the similarity of this case to our own present case, we carried out further investigations, and in Table I the results are compared with those of Salt *et alii*.

TABLE I.

Results of Serum Lipid and Other Investigations in Case V Compared with Corresponding Investigations of Patient Described by Salt et alii (1960).

Investigation.	Results.		
	Case V.	Patient of Salt *et alii*.	Normal Range.
Fæcal fat	13 grammes per day	6·7 grammes per day	4 grammes per day
Acanthocytes	Absent	Present	—
Serum	Clear, colourless.	Clear, colourless	—
Serum lipid levels:			
Total lipids	200 mg./100 ml.	80 mg./100 ml.	470–860 mg./100 ml.
Cholesterol	58 mg./100 ml.	22 mg./100 ml.	120–250 mg./100 ml.
Phospholipid	142 mg./100 ml.	45 mg./100 ml.	160–310 mg./100 ml.
Carotenoid	0	0	0·4–1·2 µg./100 ml.
Chylomicron count after fat meal	30 particles per field	0	200 particles per field
Serum lipoprotein levels:			
α-lipoprotein	Approximately 50% of normal	Low	—
β-lipoprotein	Approximately 50% of a normal control	0	—

It can be seen that although the total lipid, cholesterol and phospholipid levels in the present case are all reduced, carotenoids are absent, and the chylomicron count is greatly diminished, acanthocytes are not present. These have been searched for on three occasions without success. Beta-lipoprotein is not completely absent, but its level is reduced to about 50% of normal, as also are the α-lipoprotein levels. This reduction in the lipoprotein levels has been demonstrated by a turbidometric method using a dextran sulphate reagent and by semi-quantitative immunological and immuno-electrophoretic methods, and has also been confirmed by Salt in Birmingham using paper electrophoresis. Preliminary testing of the β-lipoprotein content of the serum in the parents and siblings of the present patient does not reveal any abnormality.

There are therefore some differences in these two cases, although the mucosal pictures look identical. Salt *et alii* postulate a primary genetic defect in synthesis of β-lipoprotein. Is the present case (Case V) a variant of this condition or is there another explanation? We would like to suggest that the primary defect lies in the synthesis of chylomicrons within the mucosal cell. Basic information regarding this stage of fat absorption is incomplete, but it is known that glycerides and fatty acids, phospholipid, cholesterol and protein all take part in their formation. This patient is undergoing further investigation.

CASE VI.—This was a case of acrodermatitis enteropathica. It has been described in detail elsewhere (Kelly and Anderson, 1960) and will be recorded here very briefly. Acrodermatitis enteropathica is a curious condition which, once seen, can probably be recognized again easily (Figure VIII) by the characteristic pattern of the skin lesions. The patient was a boy, aged 8 years, when first encountered by us, but at the age of 9 months he had begun to lose his hair, to pass frequent loose, pale stools and to have reddened, bullous, scaly skin lesions on his face, around his eyes, nose, mouth and all other body orifices and on the extensor surfaces of his forearm, legs, hands and feet. The finger and toe nails disappeared and there was no hair at all on the body. For seven and a half years these skin and bowel symptoms had persisted, waxing and waning, but never clearing up sufficiently to allow the boy to go to

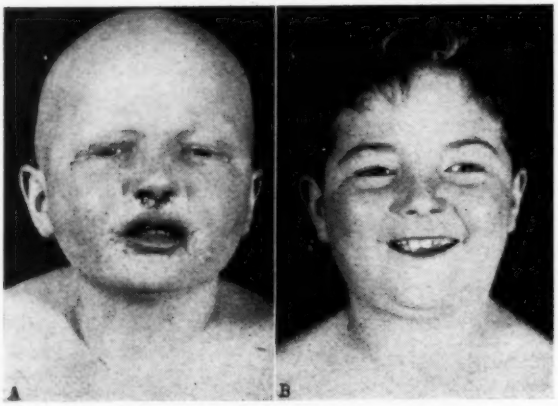

FIGURE VIII.
Case VI. A: Acrodermatitis enteropathica. Child before treatment. B: Child after treatment.

school, or even to walk very much. Investigation of the intestinal tract revealed a mild steatorrhœa (4·5 grammes of fat per day being passed in the stool); pancreatic enzymes were estimated in the duodenal aspirate, and although the content of lipase and amylase was normal, the trypsin level was persistently reduced. This condition is rare, but between 20 and 30 cases have been described. It is known to have a familial basis and each case resembles the others very closely. The ætiological basis is unknown, but the condition has been demonstrated to respond to the drug "Diodoquin" given orally. The skin lesions heal, hair grows and malabsorption disappears as the drug is exhibited. This patient was given "Diodoquin" in dosage of 1500 mg. daily and Figure VIII demonstrates the result. He has now been taking the drug for four years and remains well, with hair well grown and no skin or bowel symptoms. Even if several doses of the drug are missed the skin lesions begin to appear and the bowel motions become looser. It seems likely that this disease may have some specific metabolic basis as it is familial, responds completely to one drug and all possible infective causes have been eliminated. It also seems likely that the defect is associated with skin and mucosal surfaces, as these are the only ones affected. "Diodoquin" is a poorly-absorbed drug, but is known to be a protozoal poison. However, there is no clue as yet to its action in this disease. Recently a jejunal biopsy has been obtained from this boy, by the use of a Crosby Capsule, but the villous pattern and the mucosal surface were quite normal. However, he was taking the drug at the time and was quite well.

Undetermined Causes.

There remains a group of five children whose steatorrhœa is unexplained. In one baby severe urinary infection with pyonephrosis was also present and caused death before complete investigation was performed, and no post-mortem examination was made. Another child suffered from portal hypertension and liver cirrhosis, but passed out of our care before being completely investigated. The remaining three children are still under investigation. One, a mentally retarded girl, aged seven years, with an apparently sudden onset of steatorrhœa six months before, does not at present fit into any of the categories described, and apart from the gross steatorrhœa no other abnormality has been found. Mucosal biopsy reveals no abnormality. The remaining two children are thought clinically to be cases of mild cœliac disease, but the biopsy specimens show only blunting and broadening of some villi with no change in others. The surface mucosal cells are flattened over several broad villi, but not over others. At present a trial of gluten-free diet is in progress. If this is successful and a further biopsy shows improvement in the pattern, this will reinforce the diagnosis, but will indicate that in a few mild cases of cœliac disease mucosal change may be minimal and difficult to interpret without considerable experience. In most cases the changes are very marked, but there is a definite gradation and this can be seen particularly in the recovery stage (Anderson, 1960).

Summary.

An investigation into the causes of steatorrhœa by one group of workers reveals that of 266 patients investigated, 93 suffered from cœliac disease, 139 from fibrocystic disease of the pancreas and 34 from a wide variety of other conditions.

A good clinical knowledge of the two main conditions, with the use of certain relevant confirmatory tests, will enable the diagnosis to be made readily. For the remainder a physiological approach to small intestinal function is essential and it may be necessary to employ a range of investigations.

Among the less common causes, disturbances of many physiological aspects of the function of the small intestine were encountered, including its anatomy, length, motility, exocrine secretions and mucosal alterations.

Acknowledgements.

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THE ELECTROCARDIOGRAM QT AND RHEUMATIC CARDITIS.[1]

By D. C. FISON, M.B., B.S., M.Sc.,
Medical Superintendent, Brisbane Children's Hospital, Brisbane.

THE *QT* duration, or, as it is sometimes called, the period of electrical systole, has had a variable history of importance. It became a measured entity in electrocardiographic studies well after the establishment of the *PR* interval, then later it began to vie with this measurement in significance, especially with regard to changes in rheumatic carditis. Later again, probably because of difficulty in measuring it accurately and the uncertainty

[1] Read at a meeting of the Australian Pædiatric Association on April 21, 1961, at Canberra.

of what was normal, it retired gracefully into oblivion so that some electrocardiographic mounting forms do not list it among the components to be measured as a routine.

However, I believe it is now well established that while the *PR* interval and the *QRS* complex show well disorders in the conduction system of the heart, it is the recovery

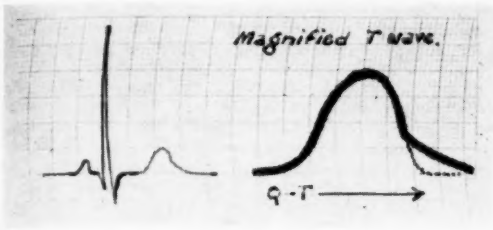

FIGURE I.

period involving the *T* wave, and with it the *QT* duration, which is most sensitive to any toxic effects on the myocardium; and I shall endeavour to show that, when measured with care and compared with accurate standards, the *QT* interval will give its modest addition to the accumulated data on which we diagnose rheumatic carditis.

have also been made to construct a unit, the best known being the *QT* corrected, or *QTC* which embraces the heart rate and so is a true normal for all rates.

$$QTC = \frac{QT \text{ (as measured)}}{\sqrt{RR \text{ (or cycle length)}}}$$

This for normal hearts is given as $0{\cdot}38 \pm 0{\cdot}04$ and 0·404 by different workers. I have found it useful, but care must be taken that *RR* (the cycle length) is an average of many complexes, otherwise sinus arrhythmia, which does not seem to affect individual *QT* values, will so upset the ratio as to make it valueless. Emanuel Goldberger has gone a step further and constructed a nomogram, on which one joins points on a *QT* scale and an *RR* scale. The nomogram not only calculates the *QTC*, but compares it with the normal value, and one can read off directly the *QT* ratio, of which 1·00 is normal. The same precaution of selecting the average cycle length is necessary as in the *QTC*.

In order to determine the effect of acute rheumatic carditis on the *QT*, I have plotted over 100 normal children's electrocardiogram *QT* measurements on a grid, indicating the *QT* on one axis and the heart rate on the other (Figure II). Also on the graph are three lines, the lower continuous one being the normal *QT* for different heart rates as given from Ashman and Hull's table, the upper continuous line being the upper limit of normal from Ashman and Hull and the broken line in between representing the normal *QT* calculated from Bazett's

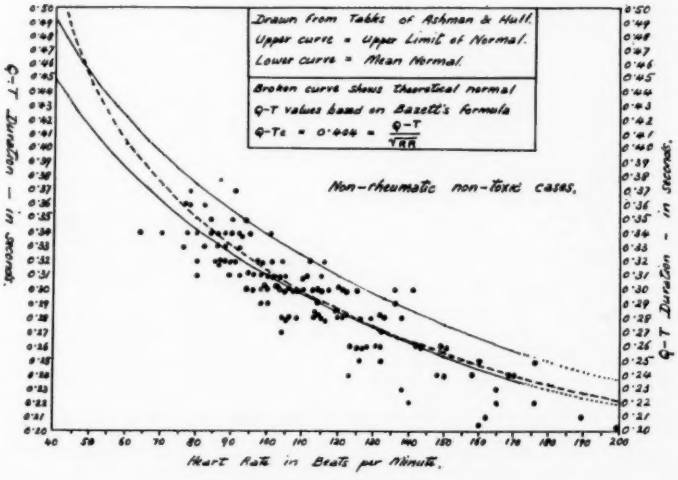

FIGURE II.

In the accurate measurement of the *QT* the following rules should be observed (Figure I): (i) always use a pair of dividers, and a lens also if one is presbyopic (by this means *QT* intervals all over the tracing can rapidly be compared and the final result read off the time scale on the tracing); (ii) choose complexes with definite *Q* waves to avoid too short a reading due to an isoelectric *Q*; (iii) discount the final wobble as the *T* wave comes down to the base line and estimate its probable time of finish were this not present, as the final irregularity is probably a merged *U* wave, which should not be included in the *QT* duration.

While the *QT* varies a little with age and sex (men and children have slightly shorter *QT* values than women), it is considerably influenced by the heart rate, being inversely proportional to the square root of the heart rate. The tables of Ashman and Hull are therefore very useful, for they give for all heart rates the mean normal *QT* value and the upper limit of normal, and are now published in most books on electrocardiography. Attempts

formula for *QTC* of 0·404. Not drawn (because not actually quoted by Ashman and Hull) would be another continuous line as far below their normal value as the upper limit is above it. This would indicate the lower limit of normal.

I confess that these cases were not of absolutely normal, symptomless children, but ones who had come to hospital with minor symptoms and fallen into the hands of enthusiastic clinicians, or who had such minor congenital cardiac defects that the electrocardiogram was completely normal and the likelihood of the *QT* being pathologically altered was remote. One will note that the plotted points fall evenly along each side of Ashman and Hull's normal line, departing from it significantly only at very high heart rates, so that their method of measurement and mine are probably similar.

Figure III shows similar plotting of the *QT* values of over 100 accepted cases of rheumatic carditis mainly in the early acute stage. You will notice in contrast with the previous diagram that in cases of rheumatic fever (i) no subjects had a *QT* value which would lie below the

lower limit of normal; (ii) the bulk of *QT* estimations are above the normal value; (iii) a large number of subjects had *QT* values above the upper limit of normal.

The diagnosis of acute rheumatic carditis rests on no specific tests, but on the assessment of a number of major and minor manifestations. Among these an increase in the *PR* interval is given mention in the criteria of diagnosis by the Rheumatic Fever Council of the American Heart Association and by the Medical Research Council of Great Britain. In my experience the measurement of the *QT* is of greater value, and I would end with the plea that it be given at least equality of weight in the diagnosis of acute rheumatic carditis.

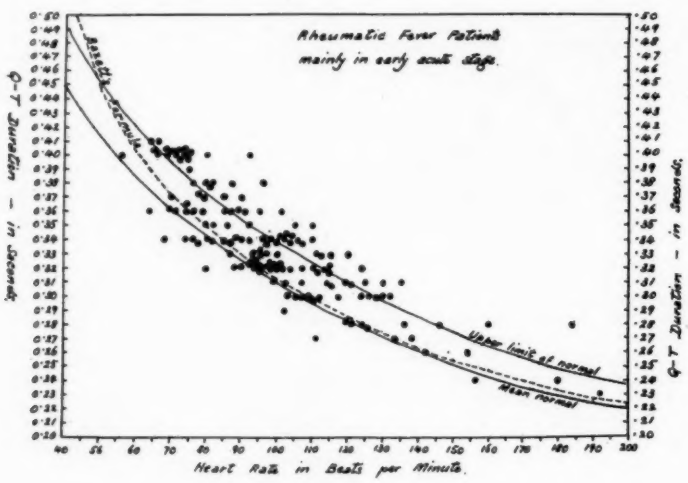

FIGURE III.

CHEMOTHERAPY AND REMISSION IN ACUTE LEUKÆMIA IN CHILDREN.[1,2]

By JOHN H. COLEBATCH, M.D., M.R.C.P., F.R.A.C.P.,
Hæmatology Research Clinic, Royal Children's Hospital, Melbourne.

LEUKÆMIA was first described and named by Bennett in Edinburgh and by Virchow in Berlin independently in 1845. Not until 16 years later was the occurrence of this disease in early life first recognized, when Virchow's pupil, Anton Biermer, recorded a case of leukæmia in a child. That was in the year 1861, just 100 years ago, and so this centenary year of 1961 is an appropriate one for the presentation of a report of progress concerning one facet of this disease in children—the results of chemotherapy for the induction of remissions.

Therapeutic measures for childhood leukæmia fall into two broad groups: (i) the more or less specific drugs for the control of the leukæmia—antimetabolites, hormones and cytotoxic agents; and (ii) general measures—blood transfusions, antibiotics and other means of controlling infections, and good general pædiatric care, including psychological support for the patients and their relatives. This paper is concerned only with the specific measures, and particularly with the trial of a régime of drug therapy in the Royal Children's Hospital over the past two and a half years.

[1] Read at a meeting of the Australian Pædiatric Association on April 23, 1961, at Canberra.

[2] This work was carried out during the tenure of a grant from the Anti-Cancer Council of Victoria.

Material and Methods.

The material from which our experience of chemotherapy has been obtained includes 26 cases concerned in a controlled trial of "Aminopterin" conducted a decade ago (Colebatch and Williams, 1950), 35 cases seen and treated sporadically between 1951 and 1956 and 117 cases that have been studied more intensively during the past four years. Each of these patients was seen by the writer and most of them were treated and followed up—an undertaking in which the writer has received assistance from a succession of colleagues.

The age and sex distributions of the clinical material in 1956-1960 are shown in Figure I. The sexes were evenly distributed; the ages of the patients at the onset of leukæmic symptoms ranged from five months to 13 years, with a definite peak at the age of three years. It is important to note that this series did include a significant number in the puberty and adolescence periods, but that there were no cases of congenital leukæmia. The cytological diagnoses were as follows. Of the total number of 105 patients, 37 suffered from acute lymphatic leukæmia and 27 from acute leukæmia probably of the lymphatic type—that is, 64 patients may be presumed to have had acute lymphatic leukæmia. Six patients had acute myeloid leukæmia, while 24 had acute leukæmia probably of the myeloid type—that is, 30 patients may be presumed to have had acute myeloid leukæmia. Eight patients had acute leukæmia to which neither label—lymphatic or myeloid—could be attached. Two patients had chronic myeloid leukæmia and one had acute monocytic anæmia. Thus in 105 consecutive cases there were 103 examples of acute or subacute leukæmia and only two of chronic leukæmia. Over 60% of all patients were regarded as having acute lymphatic leukæmia, but almost 30% were considered to have acute myeloid leukæmia. This proportion of myeloid cases is twice as great as we used to find a decade ago, but we are not yet able to assess the significance of this observation.

It is generally agreed that the interpretation of the cytological picture of an acute leukæmia may be difficult and often controversial. Our diagnosis of acute myeloid leukæmia therefore may not be accepted in all cases by other workers. Nevertheless there is no doubt from our experience that cases thus labelled have both clinical and hæmatological features that follow a characteristic pattern. We find that cases diagnosed on cytological grounds as acute myeloid leukæmia have a higher relative incidence in the age periods of infancy and of puberty, that the patients show with greater frequency signs of leukæmic

infiltration outside the hæmopoietic system, and that they usually have a greater degree of splenic enlargement. In their blood picture, early myeloid "fellow-travellers" are almost invariably present along with the blast cells; as a rule some of the blast cells show more than three nucleoli; the percentage of blast cells in the blood (commonly less than 80%) and in the marrow (commonly less than 60%) is lower than is usually found in acute lymphatic leukæmia; and in blood films stained with the fluorescein-globulin technique the percentage of abnormal non-fluorescing cells is commonly higher than in films from cases diagnosed as acute lymphatic leukæmia (C. J. Louis, 1960). There are therapeutic differences too in that myeloid cases show less initial response to steroids and 6-mercaptopurine and they have a shorter median period of survival.

The methods employed in therapeutic trials in acute leukæmia have varied little in principle over the years since anti-folic drugs were introduced by Farber in 1948. But the régimes of drug therapy have varied considerably, owing chiefly to new drugs becoming available. From 1949

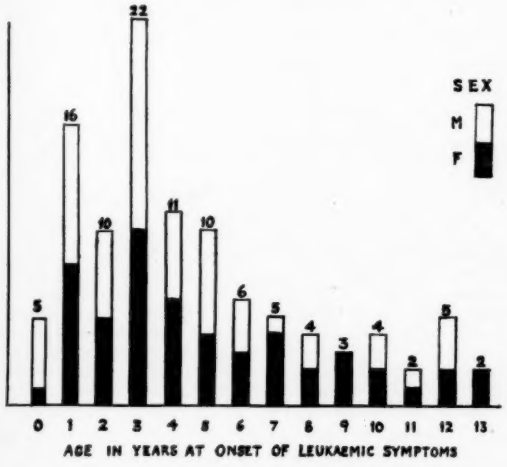

FIGURE I.

Age and sex distribution of 105 cases of leukæmia in 1956-1960. Solid columns represent females; open columns represent males.

to 1952 we used the anti-folic drug "Aminopterin" by itself in a routine daily dosage of 0·05 mg. per kilogram of body weight for one week, followed by a daily maintenance dosage of 0·025 mg. per kilogram. Then for some years hormones held pride of place—ACTH in the first year or so and thereafter the steroids. Late in 1956 we began using 6-mercaptopurine, but for the first two years this drug was not used initially; until the end of 1958 our standard régime was to start treatment with cortisone or prednisolone, and not until signs of a relapse appeared was 6-mercaptopurine commenced.

The trial now being reported began in January, 1959, since when every child in the series has been given 6-mercaptopurine from the start of treatment. Until July, 1959, prednisolone was also given to each patient from the start, in doses up to 2 mg. per kilogram of body weight per day. The dosage of 6-mercaptopurine in the earlier cases was the orthodox one of 2·5 mg. per kilogram per day. However, before long the possibility of getting a more rapid control of the disease with higher doses led us to adopt the policy of giving 6-mercaptopurine in a dosage of 4 to 5 mg. per kilogram per day for the first four days together with prednisolone at a starting level of 2 to 3 mg. per kilogram per day. With the combination of these two drugs in high dosage, often continued in only slightly reduced dosage for several weeks, good initial responses were obtained, but we had some unhappy experiences with the later development of uncontrollable staphylococcal infections. A further variation of the régime was thus indicated.

For the past 20 months we have adopted the following standard régime for all new cases of leukæmia. Chemotherapy is begun with 6-mercaptopurine, 5 mg. per kilogram per day for the first four days, followed by 2·5 mg. per kilogram per day indefinitely. Whenever neutropenia or thrombocytopenia is present in more than a minor degree, prednisolone is also given, initially in a dosage of 2·5 to 3 mg. per kilogram per day, and this dosage is reduced rapidly as soon as the neutrophils and platelet numbers are rising satisfactorily, the aim being to discontinue this drug within three weeks whenever practicable. When eventually the signs of a relapse appear, unrelated to any intercurrent infection, the 6-mercaptopurine is discontinued. At this stage an anti-folic drug is commenced, often after allowing a bridge period of seven to 10 days, during which prednisolone may again be used temporarily.

In the past six months we have undertaken a trial of "Endoxan" or "Cytoxan", a cyclophosphamide of nitrogen mustard, given both orally and intravenously. We have used this drug chiefly in the terminal stage after an anti-folic drug has failed to keep the leukæmia under control. Its possibilities merit further study in the treatment of lymphosarcoma and reticulosarcoma, but for the ordinary case of acute leukæmia it is probably inferior to the three drugs already mentioned. Chlorambucil, "Nitromin" and actinomycin-D have also been used for lymphosarcoma associated with leukæmia, but their beneficial results have been short-lived in our experience to date. "Myleran" has proved useful in the two cases of chronic myeloid leukæmia, and unexpectedly so in two of the earlier cases of subacute myeloid leukæmia. Radiotherapy has also been used with benefit in our cases of chronic leukæmia and of lymphosarcoma.

Results of Chemotherapy.

There are at least two ways in which the effects of anti-leukæmic chemotherapy must be assessed. The results are contained in the answers to the questions: how successful is chemotherapy in producing an initial remission, and how long do the remissions last or how long does the patient survive? A third question, most important from the humanitarian point of view, is: how well is the patient during the extension of life which chemotherapy provides?

The outcome of treatment for leukæmia in childhood must be viewed in perspective by contrasting it with the natural course of this disease, and a living picture of this is becoming difficult to produce for the students and residents in hospitals where chemotherapy is widely used. It is therefore helpful to refer to the data from 65 patients who died of leukæmia in our hospital between 1938 and 1948 (Table I). The average duration of life

TABLE I.

Average Period of Survival of Children who Died of Leukæmia in Hospital (1938–1949).

Cytological Type.	Number of Patients.	Average Survival Period in Weeks.
Lymphatic	33	23·1
Myeloid	10	7·0
Monocytic	3	49·0[1]
Unspecified	19	2·25
Total ..	65	7·2

[1] Including one patient with ? chronic monocytic leukæmia who lived for 88 weeks.

was not quite two months. Selection may have produced an adverse bias in this series as it does not include patients who died at home. However, in the therapeutic

trial conducted in 1949-1950 (Colebatch and Williams, 1950) the average survival period in the untreated control cases was only slightly longer—10 weeks. Most patients given only blood transfusions and antibiotics fail to regain good health even for a few weeks, and the incidence of natural complete remissions reported in large series has generally been less than 10%.

When the anti-folic drugs were introduced in 1948, this gloomy picture was brightened, almost dramatically. With "Aminopterin" therapy in 1949-1950 we obtained some improvement, both clinically and hæmatologically, in each of the first 15 cases, and the median survival period was five months, though this did necessitate lengthy periods of hospitalization. Present-day methods of treatment and of analysis make these earlier attempts appear lumbering and the results disappointing.

We have now adopted in general the strict criteria for the evaluation of remissions which were agreed upon in America in 1956. Remissions are evaluated on the basis of responses obtained in four categories—the symptoms, the clinical signs, the blood picture and the bone marrow picture. In each category three grades of response are recognized—grade 1: excellent; grade 2: fair or partial; grade 3: poor or no response.

CRITERIA FOR EVALUATION OF REMISSIONS.
(Adapted from Bisel, *Blood*, 11: 676 (1956).)

D. *Symptoms*:
1. None ascribable to leukæmia—fever, anorexia, lassitude, limb pains, sore mouth, etc.
2. Definite improvement but some symptoms persisting.

C. *Signs*:
1. No evidence of leukæmic infiltration—spleen, glands, thymus, bone tenderness, stomatitis, etc.
2. At least 50% decrease in size of organ with greatest leukæmic infiltration.

B. *Blood*:
1. Return, for more than one month, of:
   a. hæmoglobin level to 11 grammes per 100 ml., or 10 grammes per 100 ml. for those under 2 years,
   b. neutrophils to 1,500 per cubic millimetre,
   c. platelets to 100,000 per cubic millimetre, and
   d. freedom from blast cells.
2. Significant improvement for more than one month, for example, hæmoglobin level at least 9 grammes per 100 ml.

A. *Marrow*:
1. Reduction of blast cells to less than 10%, and lymphocytes to less than 20%, with essentially normal production of neutrophils, red blood cells and platelets.
2. Definite improvement, with reduction of blast cells and lymphocytes to less than 70%.

In recent years we have not done follow-up marrow punctures as a routine, so we have accepted a B1, C1, D1 response as a complete remission. A grade 2 response in any of the categories disqualifies the remission from acceptance as complete, and a grade 3 response disqualifies it from acceptance as partial.

When these criteria were applied to the results obtained with "Aminopterin" alone in our early series, the incidence of complete remissions was found to have been only just over 55%. In the next period, when for the initial therapy we used steroids alone, the complete remission rate rose to about 70%, and in 30 patients in whom steroids were followed by anti-folic drugs the median survival period was nine months.

Since the end of 1958 we have treated 73 patients with 6-mercaptopurine as a routine from the start. In 23 of these cases the data were unsuitable for satisfactory analysis owing to such factors as grossly inadequate dosage, or interrupted therapy, or because the patient was lost to follow-up, usually for geographical reasons. This proportion of cases lost from the study for the purposes of evaluation may seem unduly high, but in a recent study of acute leukæmia in children by the Leukemia Chemotherapy Cooperative Study Group A in America, no less than 50% of the cases studied were lost to final evaluation for similar reasons (Heyn *et alii*, 1960).

Table II shows the remission rates in our series of 50 patients in whom the dosage of 6-mercaptopurine was more than 2·0 mg. per kilogram per day, usually in combination with prednisolone. The figures indicate that complete remissions were obtained in 80% of all cases and that complete or partial remissions were obtained in 92%. The two main types of leukæmia show a significant difference in their responses to treatment. Complete remissions were obtained in 91·4% of cases of acute lymphatic leukæmia, but in only 50% of cases of acute myeloid leukæmia.

TABLE II.
Initial Remission Rates of Patients Treated with 6-Mercaptopurine in Optimal or Possibly Adequate Dosage (more than 2 mg. per kilogram per day) ± Prednisolone.

Type.	Number of Patients.			
	Complete Remission.	Partial Remission.	No Remission.	Total.
Lymphatic	32	1	2	35
Myeloid	7	5	2	14
Unspecified	1	—	—	1
Total ..	40	6	4	50

The data in the 46 cases in which remissions occurred were also analysed to determine the speed with which these remissions occurred. Freedom from leukæmic symptoms (D1 remission) occurred within a median period of about one week (range 0 to 48 days), freedom from leukæmic signs (C1 remission) occurred within three weeks (range 0 to 123 days) and freedom from abnormalities in the peripheral blood picture (B1 remission) occurred within five weeks (range 13 to 104 days). With regard to the length of stay in hospital after treatment had begun, the median period was just under 10 days (range 0 to 31 days).

The quality of the remissions was generally most gratifying to the patients and to their parents. The children in complete remission were not only quite symptomless, but they were often described by their parents as being apparently more healthy than their siblings, and they were in all cases well enough to resume school, kindergarten and similar activities appropriate to their age. Three of the patients obtained their first remission without requiring a blood transfusion. Once a patient developed a complete remission, subsequent transfusions averaged less than three per year, and four patients did not require a second admission to hospital for leukæmia until a year or more after the first admission.

The total length of the remission obtained with treatment in this series, and the length of the period of survival from the commencement of treatment, cannot yet be fully assessed because many of these patients are still under treatment, including seven seen first in 1958-1959 and one seen initially in 1957. However, in September, 1960, a preliminary assessment was made with regard to 52 patients (including those then living); some of these had received less than 2·5 mg. per kilogram per day of 6-mercaptopurine (Figure II). In 50% of these cases the survival period was at least 14 months and in 10% it was just over two years.

The results of chemotherapy obtained in this series of 50 cases appear to be better than all those that we have seen published from other countries, with the exception of those recently reported from the Children's Hospital of Michigan, Detroit (Zuelzer and Flatz, 1960). Although they still leave much to be desired, such results do represent a considerable and encouraging improvement on the remission rate and the survival period that will occur in the absence of treatment. However, behind this

promising picture there is a darker side that merits special study. This is represented by the 10 patients in this series for whom only a partial remission or no significant remission at all was obtained. The results of a search for factors of possible significance in relation to these disappointing responses to treatment are given in Table III.

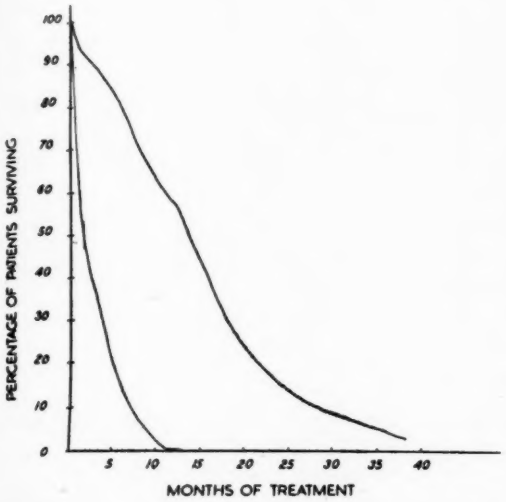

FIGURE II.

Periods of survival of patients given inadequate treatment or none (1950-1955) (left-hand tracing) compared with those given optimal or near optimal treatment (1958-1960) (right-hand tracing).

In the 10 patients with partial, poor or no remission, acute myeloid leukæmia was the cytological diagnosis in no less than eight, whereas in the 40 patients with complete remissions the incidence of acute myeloid leukæmia was only 28%. The initial white-cell count was above 10,000 per cubic millimetre in six of these 10 patients; in the majority of the other 40 patients it was below 10,000 per cubic millimetre. No less than half of these 10 patients were aged 11 years or more at the onset of leukæmic symptoms, whereas of the other 40 patients only four (one-tenth) were in this pubertal age period. Three patients had a history of leukæmia in a near relative and one patient had congenital (perhaps hereditary) mental deficiency, which suggests a genetic factor in four out of the 10 cases; of the other 40 patients, one only had a family history of leukæmia and one had a mongol sibling. Death occurred within a matter of days in three of the 10 patients, and in one of them after several days' delay in starting treatment. At least three of them received 6-mercaptopurine in a dosage which we now consider is too low to be relied upon for control of a rapidly progressing case of leukæmia.

TABLE III.

Cases with Unsatisfactory Response to 6-Mercaptopurine in Dosage Greater than 2·0 mg. per kilogram per day + Prednisolone.

Case Number.	Cell Type.	Initial White-cell Count.	Other Possibly Significant Unfavourable Factors.
		Partial Remission.	
42	Myeloid.	49,400	Family history of leukæmia.
62	Myeloid.	2,750	Pubertal; family history of leukæmia and osteosarcoma.
67	Lymphatic.	21,000	Dosage less than 2·5 mg. per kilogram per day.
69	Myeloid.	45,600	Gross stomatitis.
76	Myeloid.	93,000	Pubertal (lived 37 days).
98	Myeloid.	41,000	Family history of leukæmia.
		Poor or No Remission.	
55	Myeloid.	326,000	Pubertal; dosage less than 2·5 mg. per kilogram per day (lived 11 days).
86	Myeloid.	4,000	Pubertal; dosage less than 2·5 mg. per kilogram per day (lived 11 days).
93	Lymphatic.	8,650	Massive liver infiltration plus bacteriæmia (lived 6 days).
96	Myeloid.	7,100	Pubertal; mentally defective; died from cerebral infarction.

Although we originally used 6-mercaptopurine in the recommended dosage of 2·5 mg. per kilogram per day and subsequently increased the initial dosage to 5 mg. per kilogram per day for the first four days, it now seems to us possible that even higher dosages may sometimes be warranted for short periods. A careful retrospective scrutiny of the records of our 50 patients revealed that four of them had actually received a higher dosage in relation to body weight than was intended (much higher in two cases), yet only beneficial results were observed. The relevant hæmatological data of the two cases (Case 64 and Case 77) are presented in Table IV.

The patient in Case Number 64 was a girl, aged 10 years, who had acute lymphatic leukæmia, for which she had received intermittent steroid therapy for six months before being referred to us. She was found to have collapsed vertebræ and a rapidly advancing leukæmia with 95% of lymphoid cells in the bone marrow smears. The 11-day course of 6-mercaptopurine in high dosage led to control of the leukæmia and the girl survived for another 13 months.

The patient in Case Number 77 was a girl, aged 4 years, with acute leukæmia of indeterminate type in a well-advanced stage. She received a high dosage of prednisolone (2·5 mg. per kilogram per day) as well as of 6-mercaptopurine (4·6 mg. per kilogram per day). Despite the severe pancytopenia initially, she developed a complete remission within five weeks and is still under treatment a year later.

Summary and Conclusions.

An outline has been given of the nature of the material concerned in therapeutic trials of leukæmia in 105 children during 1956-1960, with particular regard to age, sex and cytological types.

The value of attempts to differentiate acute lymphatic from acute myeloid leukæmia has been discussed and the clinical and hæmatological characteristics of acute myeloid leukæmia as it is recognized in our hospital have been briefly described.

A history has been given of the changes in régimes of drug therapy that have occurred in our hospital between 1948 and 1960.

The criteria for the evaluation of remissions have been described.

The results of the present therapeutic régime in 50 cases have been tabulated. Complete remissions were obtained in 80% of all cases of leukæmia, in 91·4% of cases of acute lymphatic leukæmia and in 50% of cases of acute myeloid leukæmia. This incidence of remissions in acute lymphatic leukæmia is equal to the best that has been recorded in the literature—94·6% of "acute stem cell leukæmia" cases by Zuelzer and Flatz (1960).

The rapidity with which these remissions developed has been analysed. A complete remission occurred within a median period of five weeks. The median length of stay in hospital was just under 10 days.

The quality of the complete remission was such as to enable the children to return to school or kindergarten.

The length of the period of survival in this series cannot yet be fully evaluated, but the indications are that 50% of all patients will survive for at least 14 months and 10% for at least two years.

A detailed study of the 10 cases in which a complete remission was not obtained indicated that the possibly

TABLE IV.

Effects of 6-Mercaptopurine in High Dosage.

Day of Treatment.	Spleen below L.C.M.	Hæmoglobin in Grammes per 100 ml.	White Cell Count per Cubic Millimetre.	Blast Cells per Cubic Millimetre.	Lymphocytes per Cubic Millimetre.	Neutrophils per Cubic Millimetre.	Platelet Reduction.
			Case Number 64.[1]				
−8	0–1 cm.	15·0	12,100	0	9,000	2,500	None
+3	1–2 cm.	14·2	18,550	11,130	5,936	928	None
7		14·0	31,135	24,135	5,380	1,270	None
11		14·4	1,750	175	1,120	175	Slight
			6-MP discontinued; prednisolone begun				
14		12·4	1,250	100	1,050	100	Slight
19	? 0	10·8	1,900	190	1,368	342	Moderate
			6-MP resumed, 2·5 mg./kg./day				
26	0	11·2	2,700	54	1,200	1,025	None
33	0	12·4	4,200	0	2,034	1,500	None
			Case Number 77.				
0	8 cm.	8·0	27,000	17,400	8,600	268	Moderate
6		11·4	550	16	440	94	Moderate
9		9·9	1000	20	800	180	Moderate
13		7·3	900	18	630	252	Moderate
19	1–2 cm.	8·2	1,700	0	952	748	Moderate
22				6-MP discontinued			
28		11·2	1,800	0	560	1,116	Slight
35	0	12·5	2,700	0	783	1,674	None

[1] Dosage: 5·6 mg. per kilogram per day for 11 days.

[2] Dosage: 4·6 mg. per kilogram per day for 21 days, plus prednisolone and blood transfusion.

unfavourable factors were: a cytological diagnosis of myeloid leukæmia; an age of 11 or more years; an initial white-cell count greater than 10,000 per cubic millimetre; a family or personal history suggesting a genetic defect; inadequate initial dosage.

Two case histories have been described which give some support for the idea that dosages of 6-mercaptopurine of 5 mg. per kilogram per day or even more may be advantageous for short periods.

In conclusion, results of this and of other studies have shown that either anti-folic acid drugs or 6-mercaptopurine alone will produce complete remissions in at least half of all cases of leukæmia in children, that steroids alone will do so in at least two-thirds of cases, that the use of all three drugs will do so in four-fifths of all cases and in more than nine-tenths of cases of acute lymphatic leukæmia. It has also been shown that comparable progress has been achieved with regard both to the length of the patient's period of survival and to his state of health during survival.

Acknowledgements.

I wish to thank the members of the senior medical staff of the Royal Children's Hospital for their cooperation in referring patients, Dr. J. W. Perry, Dr. A. L. Williams, Miss Betty Wilson and other members of the Department of Pathology for the immense amount of laboratory work involved in a study of this kind, and the succession of colleagues who have rendered assistance in the Hæmatology Research Clinic—Dr. Margaret Horan, Dr. R. A. Chenoweth, Dr. B. Faragher, Dr. R. Evans, Dr. L. I. Taft and Dr. A. L. Clark. The encouragement as well as the financial assistance of the Anti-Cancer Council of Victoria is also gratefully acknowledged.

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ACHLORHYDRIA IN CHILDREN: SOME FOLLOW-UP EXPERIENCES.[1]

By ROBERT SOUTHBY, M.D., B.S. (Melb.), F.R.A.C.P., F.A.C.S.T. (Hon.),
Melbourne.

IN 1949 a monograph was published under the title "Achlorhydria in Children: A Clinically Recognizable Entity", in which it was demonstrated that achlorhydria in children could be seen to present itself in one of four ways, according to the particular clinical manifestations. These were diarrhœal, anæmic, colitic and allergic. During the subsequent period of 12 years many of the children so observed have been followed up and their clinical stories recorded. In addition a further group of new patients has been accumulated and an analysis of these has confirmed the findings published in the original monograph.

The second group of patients numbered 220. Achlorhydria presented as a clinical entity in 49 diarrhœal patients, in 21 anæmic patients and in 11 colitic patients. Allergy was accompanied by achlorhydria in 139 cases. Included in this group were 26 families, each with two or three children presenting clinical manifestations, particularly in the diarrhœal and the anæmic sub-groups. It is principally the results achieved and the observations recorded in following up these children for many years which are now to be presented for consideration.

Clinical Types.

I should like to recapitulate briefly the characteristic story in a typical patient of each group, together with the follow-up record of each of these four children.

Diarrhœal Group.

The patient was a male infant, aged 18 months. He was breast-fed for two months, during which time his motions were loose, green and curdy, and the bowels acted during or after every feed. By the time he had reached the age of five months the bowel actions were more frequent (from five to eight in the 24 hours), normal colour as a rule, but occasionally green and slimy with small flecks of blood. This lasts a week or more and recurs at intervals of four

[1] Read at a meeting of the Australian Pædiatric Association on April 23, 1961, at Canberra.

ILLUSTRATIONS TO THE ARTICLE BY CHARLOTTE M. ANDERSON, R. R. W. TOWNLEY, MAVIS FREEMAN and PATRICIA JOHANSEN.

FIGURE IV.

Case IV. Subacute jejunitis. Upper jejunal biopsy showing broadening of villi with cellular infiltration in lamina propria (hæmatoxylin and eosin stain).

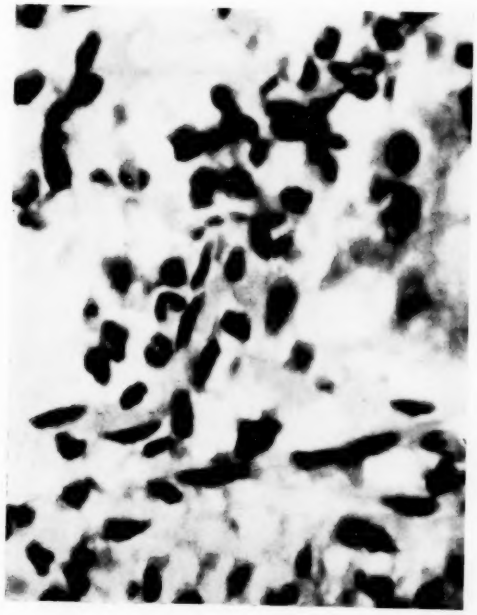

FIGURE V.

Case IV. Subacute jejunitis. Upper jejunal biopsy of lamina propria showing more polymorphonuclear cells than are usually seen (high power: hæmatoxylin and eosin stain).

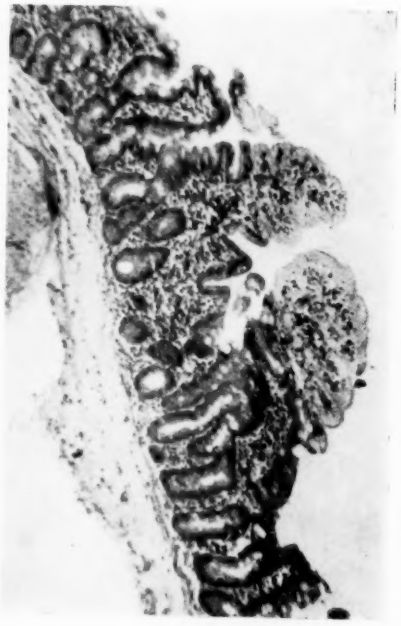

FIGURE VI.

Case V. Defect in fat transport in mucosal cells. Upper jejunal biopsy showing villi with expanded tips and large empty columnar cells (hæmatoxylin and eosin stain).

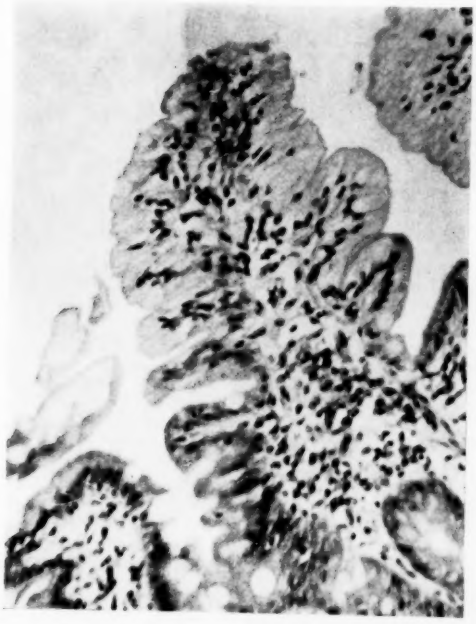

FIGURE VII.

Case V. Defect in fat transport in mucosal cells. Upper jejunal biopsy showing large empty columnar cells (hæmatoxylin and eosin stain).

to six weeks. Recently these episodes are lasting longer, and recurring more frequently. There is no vomiting and the bowels do not act during the night. Penicillin injections had been given without any response. Four minims of dilute hydrochloric acid in a mixture was given three times daily, and the response was quite dramatic, but the boy requires a basal maintenance dose of eight minims twice daily. With this he has kept well, is now eight years of age, and copes with an unrestricted diet.

Anæmic Group.

The patient is a girl, aged 12 years and nine months. For the past eight or nine months she has been easily fatigued, disinclined for food, irritable at times, unable to concentrate on lessons, exhausted by school games, looking extremely pale at times and occasionally fainting at the school assembly. She had grown considerably in the past 12 months, and recently there had been evident signs of breast development. (These children are often girls approaching puberty, and it is obvious that the combination of at least four factors — namely, physical growth, increased lessons (including homework), more strenuous games at sport and stresses of adolescence — throws a considerable strain on their constitution generally, and they are usually found to be anæmic. Iron alone is often not effective, but with the addition of dilute hydrochloric acid to the régime the resulting improvement is often dramatic.) This girl needed to be maintained on acid treatment for several years.

Colitic Group.

The patient, a girl, aged four and a half years, had suffered from recurrent attacks of diarrhœa with the passage of blood and mucus in the motions, intermittent abdominal pains, anorexia and some loss of weight. This persisted for several months. An opaque-enema X-ray study and sigmoidoscopic examination confirmed the diagnosis of a condition of ulcerative colitis. This child responded quite remarkably to dilute hydrochloric acid, which for a time had to be administered in a dose of 60 minims four times daily. At the present time, 18 years later, she still requires 20 to 30 minims of the weak acid twice daily as a maintenance dose.

Allergic Group.

The patient was a boy, aged five years, who had troublesome eczema for 18 months as a baby. Asthma supervened when he reached the age of five years and has recurred at intervals for several years. More recently he has had migraine attacks, and is subject to car-sickness. There has been a tendency to loose motions on numerous occasions. This boy has required 10 minims of the acid three times daily now for the past nine years. The mother has a skin allergy and her father is suffering from pernicious anæmia. The father always had a tendency to loose motions until he was diagnosed as suffering from achlorhydria, and he is now taking a basal maintenance dose of dilute hydrochloric acid. A younger brother of this boy has since developed both skin and chest allergies.

Other Variations.

It is quite evident that a certain proportion of these individuals require a basal maintenance dose of dilute hydrochloric acid continuously. With these the condition appears to be congenital and they need replacement therapy to maintain good health in a fashion quite comparable to the need of the cretin for thyroid extract.

In the second group these children first present their symptoms at the age of one or two years. These respond satisfactorily and some of them require treatment for a considerable time, whereas others respond quickly and appear to remain well.

Some show a tendency to relapse for no particular reason.

In a further group of older children the condition appears as a series of recurrent episodes with complete freedom in between the attacks; some are precipitated by intercurrent infection, trauma or emotional disturbances, and some occur spontaneously.

In the somewhat larger group associated with the allergies practically all the patients showed lasting clinical improvement when the particular allergic trouble (eczema, hay fever, asthma or migraine) had subsided.

A significant number of the older individuals (up to 21 or 22 years of age) required amounts of the dilute acid varying from 15 to 30 minims three times daily. Others again needed smaller amounts, and some required only five to 10 minims three times daily.

The response to acid therapy is usually prompt and with sufficient dosage the improvement may be evident in 48 hours; the dosage needs to be gradually increased if the response is not manifest reasonably soon.

Those children who require treatment constantly miss the acid very quickly when it is discontinued, relapsing even within 24 to 48 hours. It is therefore wise to make any attempt at reduction of the dosage gradually over a period of several weeks.

Administration of the Acid.

The classical method of taking the dilute hydrochloric acid was well diluted in a glass of water during the meal times. Some children will take it in this fashion for quite lengthy periods, whereas others refuse it in this form either from the initiation of the treatment or shortly after its commencement. Many therefore prefer it well diluted in lemonade, cordials or fruit drinks, or in semi-solid foods, especially in stewed fruits or puréed vegetables. Some mothers have found it to be well tolerated in tomato juice, especially if the latter is icy-cold. With a few of the older children the acid has been administered in gelatine capsules. By this means it has been well managed over long periods.

Relationship to Food.

In some instances the acid appears to be most effective and best tolerated if administered 10 or 15 minutes before meals and taken as a dose of medicine. However, most manage it quite satisfactorily over very long periods if it is taken well diluted and sipped at intervals throughout the meal. This is doubtless the most popular programme. A few of the children have definitely preferred to take the acid as a drink towards the end of the meal, or immediately after it is finished.

Duration of Treatment.

Those patients requiring acid from early infancy are more likely to need it either constantly or for very long periods. Those presenting their symptoms in the first instance in early childhood will usually need the acid for long periods, or intermittently for short periods. When the manifestations first present in older children it is more often found that the therapy is needed transiently and for short periods at a time.

Objections.

A few children have complained of a burning sensation in the throat, even with the acid well diluted, and a small number have refused to take it at all. Some claims have been made that the acid over a lengthy period has a detrimental effect on the teeth. This will seldom present as a problem if it is well diluted and taken with food. Only exceptionally has a dentist queried the practice of administering the acid to children over long periods. With an appreciable number of the children there has been some frequency of micturition in the daytime, and bedwetting at night. This subsides when the acid therapy is stopped for short periods.

Discontinuance.

When discontinuance of the acid therapy is contemplated this must be started by reducing the dosage slightly for a week or more, observing any effect, and then gradually making further progressive reductions from time to time. Some children can eventually maintain good health without the acid, but others remain well for a time and then relapse. With these the dosage must be increased until the response is satisfactory again.

Response.

The response may be quite dramatic and specific on occasions and the improvement is maintained so long

as a basal maintenance dose is continued. The children will frequently miss the acid very quickly if it is stopped suddenly, even to the extent of coming to the parents and asking for the "acid drops". Others respond more gradually and often need a larger maintenance dose.

Fallacies.

Throughout this work it has been repeatedly evident that two fallacies are occurring to which it is opportune to refer.

Fat Intolerance.

Infants or young children presenting the classical story of the diarrhœal manifestations of achlorhydria are frequently erroneously regarded as suffering from fat intolerance or fatty indigestion and placed on strict fat-free diets.

Even such dietary restrictions have little if any benefit on the frequency or the consistency of the motions.

When acid therapy is introduced these children respond in a most gratifying fashion and, having become stabilized, are able to cope normally with a full diet.

Iron Deficiency.

This presents very definitely in some infants who are artificially fed, especially should this have been necessary from birth. Such infants are usually on an adequate feeding of normal composition with a full range of vitamins, but strange as it may seem, have never been given any iron. They present a rather typical picture of very pale little individuals, somewhat spindly and of poor general tone, with an almost transparent appearance about the ears and veins showing prominently under the pale skin, especially on the scalp. In general they are not very keen about taking feedings and they have not gained weight satisfactorily. On the institution of combined iron and acid therapy the response is nothing short of dramatic and within a few weeks the infant has become transformed into a lively, active little individual, with good tone, and definite relish for food and a healthy pink tint in the skin which accompanies the marked rise in the hæmoglobin content of the blood. These babies require a continuance of the iron and acid until they are well established on a good mixed diet.

These two fallacies are mentioned because each is readily recognizable; they do present from time time, and the response in each instance is very satisfactory for the children, the parents and the pædiatrician.

This submission represents the recorded observations of an old pædiatrician throughout a number of years in practice.

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Medical Surveys.

CANCER CHEMOTHERAPY: PART ONE.

THE IMPETUS.

IN spite of the extensions of radical surgery and radiotherapy, in spite of mass education of the public, and in spite of mass radiography and cancer-detection clinics, it is apparent that only marginal improvements in the cure rate for malignant disease have been achieved. Little change has been made in the numbers of patients dying from cancer each year.

Extended radical surgery can be expected to benefit the patient with extensive local disease without distant metastasis—patients with Stage I and Stage IV lesions will derive only increased morbidity. Radiotherapy has achieved many spectacular remissions and long survivals, but many tumours fail to regress with radiation, and with others regression is often incomplete. Although the success of treatment is inversely proportional to the extent of spread at the time of treatment, over the whole range of malignant disease the cure rate will not necessarily rise if patients report earlier (Bloom, 1950; Kreyberg, 1953).

The impotence and despair one feels when faced with this disease affect most the general practitioner who manages the cancer patient in the home through all the final, hopeless phases to death, with narcotics as his only certain tool.

How simple it would be if we could find the chemical touch-stone that turned base cells into good. This dream of chemical simplicity sustains the clinical or laboratory research worker in cancer chemotherapy who sees sporadic dramatic effects, and who strives continuously to probe the significance of these results and to extend their usefulness.

THE HISTORY.

The frustration of the medical profession and the afflicted public in the presence of malignant disease is reflected in the use of every method and agent that has come to hand.

Blood-letting as a therapy for cancer has probably ceased, but the application of caustics such as podophyllin and carbolic acid continues. In 1865 Lissauer described improvement in leukæmia with Fowler's solution (potassium arsenite), and favourable reports continued as late as 1931 (Forkner and Scott).

The necrotic effects of bacterial infection were extensively investigated after Busch in 1866 observed the dramatic regression of inoperable sarcomas in two patients when they developed erysipelas. Since then various extracts from bacterial culture have been used with irregular results (Fehleisen, 1882; Spronck, 1892; Daels, 1910; Gratia and Linz, 1931; Duran-Reynals, 1935; Nauts *et alii*, 1946; Roskin, 1946; Malisoff, 1947; Cohen, 1947; Hauschka, 1948), with Coley's toxins (1936) and Shear's polysaccharides (1943) receiving the most attention. Doubtful efficacy and high toxicity have caused them all to be discarded; and their mode of action has subsequently been shown to be an effect of bacterial toxins on capillaries, producing stasis and necrosis rather than any direct action on tumour cells (Algire *et alii*, 1954).

Many sera have been developed to stimulate the reticuloendothelial cells specifically and non-specifically in the hope of inducing immunological rejection of cancer cells. However, Davis (1947) and Skapier (1947) were unable to confirm the successes in this direction reported by Bogomolets (1943) in Russia with his "anti-reticular cytotoxic serum".

More recently has been reported the use of a combination of ACTH with tetracyclines; the readiness to try any new drug reflects the inadequacy of our present agents in treating advanced cancer.

However, since 1944 new groups of agents have been developed, and this paper is devoted to a consideration of the background of the major groups that have remained in use since their original trials.

THE ACHIEVEMENT.

In some patients tumour masses regress completely with chemotherapy. Ulcerated growths can shrink and heal over; widespread melanoma deposits disappear; distressing pleural effusions and ascites absorb; large lymph-node swellings shrink, often with cessation of their obstructive effects; pain and discomfort can be relieved. In leukæmic patients who die from another cause, sometimes no histological evidence of leukæmia can be found at autopsy. Proven carcinomas of the uterine cervix, treated with cytotoxic drugs before surgery, have not been found on subsequent section of the specimen.

These remissions of disease can be quite long, but none has yet proved permanent in humans, although it is pos-

sible that chorio-carcinomas have been cured. Some individual tumours which would have been expected to grow progressively, with death of the patient in weeks, have disappeared or remained static for many months.

THE DISAPPOINTMENT.

Most patients show no evidence of tumour response to drugs. Only some 10% of patients will have any dramatic change in their tumour.

Of the others, the changes are frequently equivocal, in that tumour regresses in one area while progressing in another. Any retrogressive changes can be evanescent, and, when the patient's course is compared with the natural history of the untreated disease, it is difficult to be sure that any useful change has been wrought.

Although in individual patients rapid shrinkage of tumour masses is seen, none has yet been shown to have been cured of metastatic disease. In fact, there is as yet no firm evidence that survival time has been increased in any group of patients, though it is a strong clinical impression that this has been achieved in individuals.

In patients who respond, the time of remission can be measured in months only, not years. When regrowth of the tumour is manifest, it will not necessarily respond to the same drug or any other drug. It is convenient to consider this drug resistance as analogous to bacterial resistance to drugs, but such a concept has not yet received experimental confirmation.

The choice of agents is entirely empirical, and the logical worker is distressed that he can only rationalize from sporadic successes or mass-screening techniques, and guess at possible lines of investigation.

THE DANGERS.

All the cytotoxic agents in clinical use inhibit all rapidly-growing tissues, and their effect on tumour cells might be a function of mitotic rate. In the body, cells undergoing the most frequent division are those of bone marrow and of epithelial surfaces, especially in the gastro-intestinal tract; and it is on those tissues that the cytotoxic effects are most critical.

Gastro-intestinal toxicity is distressing, but bone-marrow depression can be fatal. The earliest effects are on leucocytes and platelets, and the patient forced into agranulocytosis suffers a severe and very distressing illness with ulceration and bleeding from the mouth to the anus, frequently terminating in overwhelming infection or fatal hæmorrhage. The course of this iatrogenic disease is sufficiently prolonged for the picture to be firmly imprinted in the mind of the physician who produced it.

Such toxicity is not necessarily the result of uninformed or foolhardy prescribing, for leucopenia can progress for three or four weeks after a single dose of some agents.

In the face of severe leucopenia and platelet depletion, little therapy is available to revive the depressed bone marrow, and treatment is mainly directed at the prevention of the dire consequences of their absence.

Further, fœtal death or multiple developmental abnormalities can be induced when the agents are used in malignant disease complicated by pregnancy (Sokal and Lessmann, 1960).

THE AGENTS.

Three main directions of research into tumour-inhibiting agents have proved profitable.

These have produced drugs of the mustard group known as alkylating agents, antimetabolites (particularly against folic acid and purines), and antibiotic derivatives.

The mode of action of none of these is certain, and the separation of the groups may prove to have only an historical significance.

In addition, a host of agents undergo screening tests annually, and an indication will be given of some of the techniques used in their evaluation.

Hormone administration and deprivation techniques will not be discussed here, for these subjects are fully treated elsewhere. (However, it can be said that their effects are frequently as dramatic as those of the cytotoxic agents; and they should be used first in appropriate cases, for their iatrogenic complications are fewer and not as lethal.)

Nor will radioactive isotopes such as those of iodine and phosphorus be discussed, for the writer has no personal experience of their use.

Alkylating Agents.

The term alkylating agents has come to be used for all drugs of the nitrogen mustard group and their derivatives. Literally, alkylation implies making alkyl — that is, alcoholic—radicles. In the context of these agents, the term applies to a nucleophilic substitution by which the reactive drug, rich in electrons after dissociation in solution, combines with some other compound in the body, usually through an oxygen, nitrogen or sulphur atom. The groups of compounds showing biological alkylating properties are sulphur mustards, nitrogen mustards, ethyleneimines, methanesulphonates, epoxides and β lactones. Those in clinical use are nitrogen mustards, ethyleneimines, methanesulphonates and epoxides, and the first two of these are discussed at greater length.

Nitrogen Mustards.

History.—When World War II began, a research programme was drawn up in Great Britain and the United States of America to study the biological effects of vesicant poison gases such as lewisite and mustard gas (di-chloroethyl sulphide) in order to develop antidotes. Mustard gas had been observed by Stewart (1918) and the Krumbhaars (1919) to depress hæmatopoiesis and to hinder the appearance of tar-induced tumours on rat skin (Berenblum, 1929); attempts were made to use it clinically in patients with carcinoma of the breast by Adair and Bagg in 1931. The same hæmatopoietic depression was seen when nitrogen was substituted for the sulphur of mustard gas forming the compound methyl-bis(β-chloroethyl)amine hydrochloride, known by the military code name of HN2 (Figure I), and the compound methyl-tris(β-chloro-ethyl)amine hydrochloride, known as HN3. Since lymphoid tissue was susceptible to the nitrogen mustards in sublethal doses, these agents were used clinically in patients with malignant lymphomas and other neoplastic diseases by Gilman *et alii* (confidential military communication, 1943, unpublished) and Wilkinson and Fletcher (1947). Extending Gilman's work, Jacobson *et alii* (1946), Goodman *et alii* (1946), Karnofsky *et alii* (1947) and four other groups cooperated under conditions of military secrecy in a clinical assessment of the drug. This group study of 160 patients was published by Rhoads (1946); between 1947 and 1949 more than one hundred institutions participated in a cooperative study, since when the drug has been in widespread and increasing use.

Mechanism of Action.—The means by which the nitrogen mustards and other alkylating agents inhibit tumour growth are unknown. The evidence of their mode of action can be discussed at biological and chemical levels. The biological effects of the alkylating agents on cellular function are eight in all. Firstly, there occurs a depression of blood-cell production in normal and leukæmic patients. All the hæmatopoietic system is affected and can proceed to total aplasia. The effects on peripheral blood are seen earliest in the cells with short lives, particularly platelets and polymorphonuclear leucocytes (Elson *et alii*, 1957). Secondly, mitotic arrest occurs during interphase, with continued nuclear growth and fragmentation (Bodenstein, 1947), and during metaphase, with pyknosis (Dustin, 1947). Thirdly, there is inhibition of growth and often complete regression of experimental tumours in animals (Burchenal *et alii*, 1951; Buckley *et alii*, 1952; Suguira *et alii*, 1957). Mutagenic effects occur as chromosome breaks similar to the effects of irradiation, mutations in *Drosophila* and reverse chemical mutations in

bacteria (Auerbach, 1958). Mutations were induced in *Penicillium notatum* by Stahmann and Stauffer (1947) and in *Neurospora* by Horowitz *et alii* (1946). Fifthly, multiple developmental abnormalities or teratogenic effects are produced in fœtuses of rats and mice (Murphy *et alii*, 1958), affecting the skeleton, the soft tissues and the heart. Carcinogenic activity has been indicated by Boyland and Horning (1949), Griffin *et alii* (1950), Shimkin (1954) and Walpole (1958). Seventh, inactivation occurs of the pneumococcus-transforming principle, mainly composed of deoxyribonucleic acid (Herriott, 1948) and the *Hæmophilus influenzæ*-transforming principle. Zamenhof (1956) found

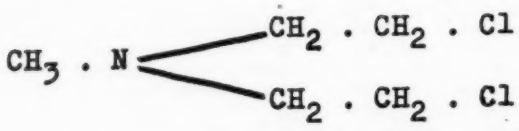

FIGURE I.

Methyl-tris(β-chloro-ethyl)amine hydrochloride.

a correlation between the activity on the transforming principle and on the Walker rat carcinoma, and he suggested that the carcinostatic action was due to the inactivation of cellular DNA. Last, there is suppression of antibody formation. This effect is probably produced by gross involution of the reticulo-endothelial system. Incidentally, this provides a techinque for prolongation of homograft survival, and cytotoxic agents have been used in conjunction with renal homotransplantation.

The effects are produced by minute doses of mustard, which suggests that the drugs are toxic to nuclear and not cytoplasmic functions (Auerbach *et alii*, 1947). The similarity of the biological effects of the mustards to those of irradiation has led to the term "radio-mimetic" to describe them as a group. More closely, many of the effects can be traced to alteration in nuclear deoxyribonucleic acid. Most theories of induction of cancer meet at the replication mechanism of deoxyribonucleic acid to explain the genetic transference of the different characteristic. Among later groups of cytotoxic agents will be seen more sophisticated attempts to change nuclear deoxyribonucleic acid. The biological evidence throws some light on where the agents act. The chemical evidence approaches the question of how they act. Alkylating agents are described as monofunctional or polyfunctional, according to whether one or more reactive groups are formed in solution. At the chemical level, Stein *et alii* (1946) have demonstrated that the stable crystalline nitrogen mustards are transformed to a cyclic carbonium cation in solution at the pH of body fluids with liberation of chloride anion (Figure II). This ring form (or ethylene imonium cation) will combine with many groupings, proceeding preferentially for alkylation on sulphur, then nitrogen and least readily on oxygen. Ross (1958) found a correlation between chemical reactivity and biological effectiveness on animal tumours of different alkylating agents; the likely chemical centres for reaction were ionized acid groups, sulphydryl groups and free amino groups, and on clinical correlation, the ionized acid groups seemed the most likely sites *in vivo*, for drugs mainly affecting the other groups had no biological effect. Stacey *et alii* (1958) indicated that when the number of sites available for alkylation greatly exceeded the amount of reagent (as applies in clinical dosage), the characteristic reaction is esterification of anion such as the carboxyl groups in proteins and the phosphate group in nucleic acids; and believed that the polyfunctional character of many alkylating agents enabled them to form cross-links within the molecule and between molecules. Berenblum (1949) had shown that mustard gas caused an intracellular precipitation of nucleoprotein.

In summary then, these alkylating agents are seen to affect nuclear functions, probably in various ways, with esterification of phosphate groups in DNA and cross-linking between and within molecules. There is no evidence that they are localized selectively in malignant cells rather than normal cells. The close relationship between the biological activity and chemical reactivity strongly suggests that such biological activity is the result of chemical reaction rather than a purely physical effect on the system.

Pharmacology.—The absorption, distribution and excretion of the alkylating agents are ill-defined (Philips, 1950). The high toxicity demands the use of small quantities; and the lack of sensitive methods for

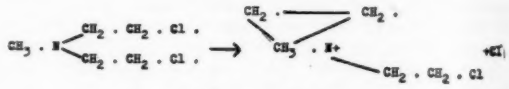

FIGURE II.

Nitrogen mustard ⟶ cyclic ethylene imonium cation and chloride anion.

qualitative or quantitative estimations has necessitated synthesizing the drug with radioisotope components. Ausman *et alii* (1959) have recently reported a chemical reaction for the detection of active nitrogen mustard and other alkylating agents in blood at concentrations as low as 0·004 mg. per millilitre. Davison *et alii* (1957) using ^{35}S sulphur mustard observed that 80% of the drug disappeared from the blood within one minute after intravenous injection, the remainder appearing stable and disappearing slowly over a period of days. About half the drug was excreted in the urine in two days as a component of at least six compounds. Skipper *et alii* (1951) studied the metabolism of ^{14}C nitrogen mustard, finding the radioactivity distributed throughout the mouse with high tissue fixation, especially in the intestine. Nadkarin *et alii* (1956) similarly found over 90% of the isotope was removed within 30 seconds. Some of the drug was demethylated (10% to 18% of the carbon being exhaled as carbon dioxide) and the enzyme responsible for this reaction was shown to be present in the microsomes of liver cells (Axelrod, 1956). The uptake in different tissues was approximately the same in both tumour-bearing animals and controls (Craig and Jackson, 1955; Nadkarin *et alii*, 1957). The alkylating agents apparently interacted with various compounds immediately after administration, and the reaction products were metabolized or excreted over several days. The variety of radioactive metabolites appearing when different portions of the drug were labelled indicated that the carrier moiety was separated readily from the alkylating groups (Smith *et alii*, 1958).

Toxicity.—The nitrogen mustards do not kill neoplastic cells specifically, but affect normal cells also. This is seen clinically where the concentration is highest or the cells are most susceptible. Local toxicity at the injection site demands that nitrogen mustard be introduced into a rapidly-running intravenous infusion. If some drug leaks outside the vein a painful induration results, which can proceed to necrosis and ulceration with thrombophlebitis. A metallic taste may be noted immediately after injection. After a delay of half an hour to eight hours salivation, followed by nausea and vomiting, occurs, and can persist for as long as two days, commonly with anorexia, weakness and headache in addition. These symptoms are reduced by pyridoxine (Shullenberger *et alii*, 1949) or phenobarbitone (Kennedy and Aub, 1949). Larger doses can cause diarrhœa and hæmorrhagic necrosis of small bowel mucosa, and bleeding from nose and gums. The severity and duration of these symptoms are less in children and those heavily sedated before injection with hypnotic doses of barbiturates.

Lymphocyte and monocyte counts begin to fall within 24 hours and continue to fall for about a week, rising to normal levels again by two weeks. Neutrophil counts drop after 48 hours and are progressively depressed for two to three weeks, after which recovery takes another two weeks. Daily leucocyte counts are advisable during

treatment (Haddow, 1951). Platelet counts fall within two to three weeks and usually recover within a further week. Red-cell counts fall less severely within two to three weeks, and reticulocyte counts are also depressed; recovery takes a further two or three weeks. Serial bone-marrow smears show that all elements are affected, and with large doses the cellular damage can proceed to almost total aplasia. Recovery of the marrow is not complete for six weeks (Jacobson *et alii*, 1946). With prolonged perfusion through an isolated circuit, local toxicity is seen as limb œdema, erythema and depilation, and, with increasing dosage, skin and muscle necrosis.

FIGURE III.
Triethylene thiophosphoramide (thio-TEPA).

No impairment of hepatic or renal function has been observed, in spite of the high flows of the drugs through these organs seen in radioactive tracer studies. However, Ehrlich (1910) observed renal papillary necrosis with lethal doses of an ethyleneimine. Various early derivatives of the nitrogen mustards produced dizziness and temporary psychoses (Burchenal, 1958) and a "waltzing" syndrome can be induced in rats and mice with lethal doses of nitrogen mustard (Sternberg *et alii*, 1958).

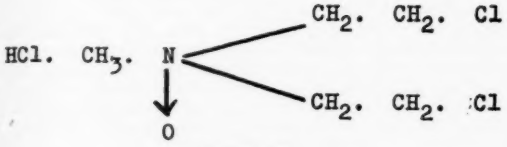

FIGURE IV.
"Nitromin."

Administration and Dosage.—HN2 hydrochloride is a white, crystalline powder, water-soluble, and stable in an acid medium. In aqueous solution it loses activity slowly, and in alkaline solution iminizes rapidly. The drug is used as a fresh solution containing 1 mg. per millilitre of saline. It is usually given as an intravenous injection by needle, and can be injected rapidly, but the chance of local leakage is less if it is injected into a fast-running intravenous infusion. HN2 can be injected into pleural effusions (Kent and Moses, 1951), into the pericardium and peritoneum (Weisberger 1958) and into arteries (Klopp *et alii*, 1950). It is not given orally, but during World War II seven volunteers were given HN3 by mouth, with moderate gastro-intestinal symptoms and sufficient leukopenia to indicate absorption (Jager *et alii*, 1943). The single-dose LD_{50} of HN2 given by intravenous injection in man is estimated at 1·0 mg. per kilogram of body weight. The usual therapeutic dose is 0·1 mg. per kilogram intravenously daily for four days. A further course can be given in one to two weeks if the peripheral blood has been little affected. The amount injected into body cavities or into arteries is a single-shot dose of 0·4 mg. per kilogram, and systemic toxicity is less when the drug is given by these routes.

Ethylene-imines.

History.—Triethylene melamine (TEM) was first synthesized in Germany during World War II for use in a commercial process for improving the finish of rayon fabrics. In a screening programme with agents capable of reacting with amino-groups, Rose *et alii* (1950) found some inhibition of growth of Walker rat carcinoma 256. Burchenal *et alii* (1950) investigated these agents in view of their reactivity with cellulose and their structural relationship to transformation products from the hydrolysis of nitrogen mustards, and found inhibition of animal tumours. The phosphoramide derivatives were found to be effective against mouse sarcoma 180 (Buckley *et alii*, 1951), rat sarcoma (Crossley *et alii*, 1952) and mouse leukæmia (Burchenal *et alii*, 1952). Clinical testing began with TEPA (Farber *et alii*, 1953) and other derivatives DEPA and ODEPA. In 1952 Personeus *et alii* showed that thio-TEPA inhibited the development of pulmonary metastases in breast carcinoma in rats, and this compound has been found active against other experimental animal tumours

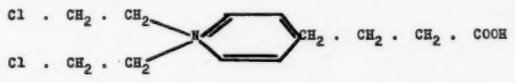

FIGURE V.
p-(di-2-chloro-ethyl)amino-phenylbutyric acid, CB 1348, chlorambucil, "Leukeran".

(Sparks *et alii*, 1953; Shay *et alii*, 1953; Sugiura and Stock, 1955). Clinical use of thio-TEPA was first reported by Shay (1953) and many reports have followed (for example, Bateman, 1955; Wright *et alii*, 1957 and 1958). Thio-TEPA (TSPA, triethylene thiophosphoramide) has largely replaced the other ethyleneimines in clinical practice because of its greater stability and therapeutic effectiveness, combined with lower toxicity than TEM. (However, Bolton finds that TEM is more likely to be effective than TSPA, and that its toxicity is largely avoidable.) A new derivative, PEDP, is presently under study (Allison *et alii*, 1959).

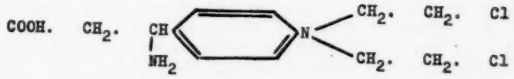

FIGURE VI.
Di-2-chloroethyl-*p*-aminophenylalanine, CB 3025, melphalan, sarcolysin, phenyl-alanine mustard, PAM.

Mechanism of Action.—Triethylene thiophosphoramide, in its structural relation to the hydrolysis products of the nitrogen mustards, is assumed to have a similar alkylating action, and in experimental work follows the same patterns of biological effects (Smith *et alii*, 1958; Murphy *et alii*, 1958). It must be noted that, although the effect of this agent appears to be on nuclear material, and maximal during mitosis, the apparent effect of a dose can persist long after the agent would be presumed to have been inactivated and/or excreted.

Toxicity.—Immediate toxic side-effects with thio-TEPA are most uncommon. Occasionally anorexia, nausea or vomiting is seen. The only significant toxic effect is depression of white-cell and platelet production which can occur with as little as 10 mg. of thio-TEPA (Wright *et alii*, 1958). The white-cell count commonly falls in two to four weeks and recovers in one to three weeks. Thrombocytopenia is uncommon and is preceded by leukopenia (Bateman, 1955). Such hæmatopoietic depression occurs in about half of the patients treated (Wright *et alii*, 1958; Moore, 1958). No therapy is available to accelerate the return of marrow function; during the recovery phase, antibiotics and fresh blood transfusions are used as necessary. Concomitant steroid therapy has not been shown to be useful in accelerating return of marrow function, but has some effect in reducing platelet depletion. One clinical trial indicates that steroids given at the same time as the alkylating agent can reduce the resulting degree of marrow toxicity.

Administration and Dosage.—Triethylene thiophosphoramide (thio-TEPA, TSPA) is dispensed as a sterile white crystalline powder soluble in water or saline. The commonest route of administration is the intramuscular one, and doses are from 10 to 50 mg., given at weekly intervals. The white-cell count must be checked before

each injection, for it is unwise to continue treatment with a white-cell count below 5000 cells per cubic millimetre; consequently, no prescribed course of treatment can always be adhered to. Treatment is continued for at least three months before lack of sensitivity can be established; however, improvement is usually noted between one and four weeks (Wright *et alii*, 1958). The initial dose must be reduced for older patients, for those in poor condition and for those previouly irradiated. It is not necessary to push dosage to toxic limits to achieve a tumour-inhibitory effect. The same dose is used in intravenous injection. Thio-TEPA can be injected directly into tumour

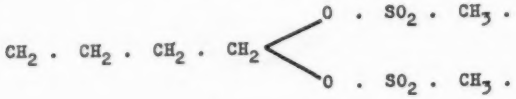

FIGURE VII.
Dimethanesulphonyloxybutane, busulphan, "Myeleran".

masses. The solution has a pH of 7·8 to 8·0, and is compatible with procaine hydrochloride. Larger doses can be given by this method (Bateman, 1958), and clearly the local concentration of drug is much higher. Intra-arterial injection has been used by repeated needle puncture, and by injection through an indwelling intra-carotid catheter in patients with cerebral tumours. This drug has also been injected directly into brain tumours through a burrhole (Davis, 1958). Intrahepatic injection via the portal vein has been safely used at the time of primary surgery. Intrapleural and intraperitoneal injections are useful in controlling effusions (Bateman *et alii*, 1955; Leone *et alii*, 1958). The usual dose is 30 mg. in 25 ml. of saline instilled immediately after aspiration of the effusion. Thio-TEPA can be given orally at the rate of 5 to 10 mg. daily. Absorption evidently occurs, for bone-marrow depression can follow oral use. Unlike the dramatic effects that nitrogen mustard can produce, the response to thio-TEPA is slow and progressive, not becoming apparent for two to three weeks.

Other Mustards.

Many variants have been synthesized around the nitrogen mustard principle to increase the specificity of action on tumour cells and to decrease the toxic effect on marrow function. "Nitromin" was derived from the oxidation products of nitrogen mustards (Stahmann and Bergmann, 1946); CB 1348 (chlorambucil or "Leukeran") was selected from a group of water-soluble aromatic mustards (Everett *et alii*, 1953); CB 3025 (phenyl-alanine mustard) was synthesized by Bergel and Stock (1953) to provide additional antimetabolite functions, and similarly 2-naphthylamine mustard (CB 1048 or R 48) and uracil mustard. Cyclophosphamide is a diphosphoramide ester of nitrogen mustard. Russian workers have produced several chloroethylamines, a methylamine, a pyrimidine and a chloropropyl mustard (Larionov, 1956). "Myleran" is a methanesulphonate, a derivative of a group showing alkylating properties *in vitro* (Ross, 1958). Epoxides have also reached the stage of clinical trial, in particular, diepoxypropylpiperazine and epoxypropidine.

"Nitromin."—This oxide of nitrogen mustard has a lower toxicity on skin and mucous membranes than the parent product, and can be injected into tumours and cavities without the intense necrotizing effect occurring. The drug is dispensed as a white crystalline powder soluble in saline or glucose solution. The dose range is from 0·5 to 2·0 mg. per kilogram of body weight, and the regular dose is thus about 50 mg. in 20 to 40 ml. of diluent. Administration can be parenteral or oral (when it is diluted to a 0·1% solution). Dosage schedules have not usually been as closely defined as those of nitrogen mustard, but a course of about seven days is common; further courses are determined by the effect on the tumour and the bone marrow. The more gratifying results have occurred with lymphoid leukæmia, and also with Hodgkin's disease and various reticulosarcomas. Various solid tumours and their metastases have regressed, particularly seminoma and chorion-carcinoma. Further, Bateman and Carlton (1958) found regression of various tumours which had been resistant to TSPA, and Stoll (1956) in disseminated carcinoma.

Chlorambucil.—Chlorambucil was synthesized as one of various carboxylic acid derivatives in the aromatic nitrogen mustard series at the Chester Beatty Research Institute, and designated CB 1348 (Haddow, 1954). Haddow (1952) established its effect on Walker rat carcinoma 256. Since then its place in the treatment of lymphomas and lymphoid leukæmia has been established (Galton *et alii*, 1955; Ultmann *et alii*, 1956), and Gumport *et alii* (1958) showed marked effects also in ovarian carcinoma. The drug is given orally at the rate of 0·2 to 0·3 mg. per kilogram of body weight (about 10 to 20 mg.) daily. A plan of three to six weeks' courses is often used, but the drug can be administered continuously unless marrow depression dictates caution. Production of toxicity is not necessary to achieve a beneficial result. The toxic effects are on white cell and platelet production, with few gastro-intestinal disturbances; its advantages are that it is less disturbing to the patient than nitrogen mustard, and safer. Gumport *et alii* (1958) found that the drug could be resumed safely even after it had previously produced toxicity. Low doses are used at the beginning of therapy until it is established that the patient's marrow is not specially sensitive to the drug.

Phenylalanine Mustard.—This compound was synthesized by Bergel and Stock (1953) at the Chester Beatty Institute, with the designation CB 3025 (melphalan), and also by Larionov (1955) in Russia in its *lævo* form under the name sarcolysin. The phenylalanine chain may permit its partial incorporation in the body—for example, in melanin—and the drug has been used with variable results in patients with metastatic melanoma. This white powder is administered orally in tablet form at a dose rate of 2 mg. per kilogram of body weight, or parenterally at half that rate. In general, the drug has been disappointing in clinical use, but in isolated perfusions more success has been achieved (Creech *et alii*, 1958).

Cyclophosphamide.—Cyclophosphamide ("Endoxan") was synthesized by Arnold in 1958, and has been reported as superior to nitrogen mustard in a wide spectrum of animal cancers (Lane and Kelly, 1959). The rationale of synthesis was to provide a nitrogen mustard which would be activated at malignant cells (believed to be rich in phosphamidases), releasing an active form within the tumour. Short-term clinical studies by Ravdin *et alii* (1959) at an intravenous dose rate of 7 to 12 mg. per kilogram per week produced moderate leucopenia and good clinical response in diverse solid tumours. Matthias *et alii* (1960) used an intravenous course of 100 to 200 mg. daily followed by daily oral administration of 100 to 150 mg. Objective improvement occurred among patients with reticuloses, and toxicity was limited to leucopenia.

"Myleran".—"Myleran" is a trade name for busulphan or GT-41, first studied by Haddow at the Chester Beatty Research Institute. Animal tumour experiments showed that lymphopoiesis was not depressed by the drug, and its place is restricted in clinical practice to the treatment of chronic myeloid leukæmia (Galton, 1953; Dameshek, 1958). The drug is given orally daily in doses of 4 to 10 mg. to a total dose of 200 to 500 mg., or in courses of 25 mg. daily for four to six days. The basic daily dose rate is 0·06 mg. per kilogram of body weight. The principal side-effect is depression of platelet production, and prolonged treatment can induce myeloid aplasia.

Epoxides.—Since Ross (1950) described the biological significance of epoxides as alkylating agents, various derivatives have been screened against experimental tumours (Gerzon *et alii*, 1959; Burchenal *et alii*, 1960). Of these, epoxypropidine appears the least toxic (Miller *et alii*, 1959 and 1960), and is injected into an intravenous infusion up to a dose of 5 mg. per kilogram of body weight. The pattern of toxicity is similar to that

of nitrogen mustard, but nausea and vomiting are less in evidence. Clinical improvement has been achieved with various reticuloses. A bromopropionyl-piperazine (A8103) has been shown experimentally (Davies *et alii*, 1960) to be a more effective cancericidal agent than HN2 against Walker 256 rat carcinoma, and to be more effective against subcutaneous implants of this tumour.

(*To be concluded.*)

KENNETH R. COX, F.R.C.S., F.R.A.C.S.

University of Melbourne Department of Surgery, Royal Melbourne Hospital.

Reviews.

Modern Surgery for Nurses. Edited by F. Wilson Harlow, M.B., B.S., F.R.C.S.; fourth edition; 1959. London: William Heinemann Medical Books Limited. 8¼" × 5¼", pp. 907, with illustrations. Price: 30s.

THE fact that this surgical textbook for nurses first appeared in February, 1948, and has already reached its fifth edition in 1961, speaks for its excellence. The editor points out that no major changes have occurred in this edition, but more illustrations have been added, and many sections, including those of shock, gangrene, peritonitis and so on, have been revised.

The book covers the syllabus for the General Nursing Council for the Final State Registration Examination in England. All branches of surgery are dealt with, and there is a chapter on pregnancy and labour and their anomalies and complications. The editor points out that the prime objective of this book is to provide a textbook that will help the student nurse to understand the reasons underlying modern surgical practice, and will also be of assistance to her in her work and examinations. There is no doubt that the authors have admirably succeeded in this purpose.

The book is very well illustrated, although we often wonder whether many of the illustrations are necessary. For instance, Kocher's artery forceps, as shown in Figure III, should be seen and handled by the nurse practically. The same applies to many of the other illustrations. It should not be necessary to pad a book with unnecessary illustrations in order to make a student read it.

Neuromuscular Disorders: The Motor Unit and Its Disorders. Edited by R. D. Adams, M.D., L. M. Eaton, M.D., and G. M. Shy, M.D.; Proceedings of the Association for Research in Nervous and Mental Disease, Volume 38; 1960. Baltimore: The Williams & Wilkins Company. 9" × 6", pp. 814 with illustrations. Price: £11.

THE latest volume in this well-known series is a report of the proceedings of the Association for Research in Nervous and Mental Diseases at its meeting on December 12 and 13, 1958, in New York. It consists of 28 papers together with a verbatim record of the ensuing discussion. The papers are conveniently arranged in five groups: basic structure and function of the motor unit (five papers); experimental pathology (three papers); basic approach to clinical problems of neuro-muscular disorders in man (three papers); clinical problems (11 papers); some experimental techniques of promise in the study of neuro-muscular disorders (six papers).

There is little need to emphasize the importance and usefulness of meetings of this sort at which are assembled specialists in several disciplines—physiologists, biochemists, histologists, experimental pathologists, endocrinologists, clinicians, neurologists. Improvement in the understanding and treatment of the various muscular disorders can be best achieved by a continual exchange of ideas between all those who are interested in this subject. The Association has been fortunate in obtaining contributions from distinguished workers in every field related to these diseases. However, the contributions as printed are substantially longer than the oral contributions, while some contributions were not read at all.

The book can be regarded as "an authoritative summing-up of all neuromuscular disorders", in the words of the president of the Association. However, because of recent conferences on myasthenia gravis and muscular dystrophy, these two topics do not receive the same attention as others; nevertheless two papers deal specifically with the former topic and three with the latter.

There is a strong emphasis on the experimental study of muscular diseases throughout. In the past considerable attention has been devoted to muscular diseases in animals, chiefly because for most human muscular diseases there are animal diseases with clinical and pathological similarities. However, these similarities may be misleading, whilst myasthenia gravis is one disorder not found so far in animals. In recent years there has been an increased endeavour to study human muscle directly. The last six papers in the volume deal with the application of various techniques to human biopsy material—tissue culture, intracellular electrical recording, enzyme studies, fluorescent antibody staining, chemical analysis. These techniques represent the most promising approach to these problems.

There is something in this book for both the clinician and the experimental scientist. Although it is regrettable that the book should appear in Australia so long after the original conference, it is nevertheless a most valuable summary of the present position in this field.

Quantitative Cellular Hæmatology. By J. M. Yoffey, D.Sc., M.D., F.R.C.S. (Eng.); 1960. Springfield, Illinois: Charles C. Thomas, 1960; Oxford: Blackwell Scientific Publications Ltd., 1961. 9" × 6", pp. 136 with illustrations. Price: 44s. (English).

THE author of this monograph has devoted many years to the study of lymphoid tissue and the bone marrow, and already has been co-author of a book on the subject of lymphatics and lymph and lymphoid tissue. The present work is concerned largely with quantitative studies of lymphocyte production, and many of the results quoted have come from experiments performed in the author's own laboratories.

The first chapter is devoted to morphological details of the cells which constitute the lymphoid complex. Then follow chapters concerned with the production of lymphocytes in the lymphoid tissues and their circulation throughout the body, particularly the bone marrow. Techniques are then described for the estimation in experimental animals of the total marrow volume, and this figure, together with standard counting methods, makes possible a calculation of the total and differential cell population in the marrow. A result of these studies was the unexpected finding of a very large lymphocyte pool in the marrow of some animals and probably in man. The studies suggest further that the lymphocytes are not formed in the marrow, but reach the marrow from lymphoid tissue via the blood-stream.

The question of the function of the small lymphocyte is discussed at some length, the author leaning to the postulate of Maximow, that this cell may be a temporary resting form of a primitive mesenchymal cell. The author does not dogmatize on the point, but presents also the evidence against the concept of the small lymphocyte being a stem-cell precursor. A short chapter is devoted to the undisputed rôle of the plasma cell in the production of circulating antibody. The puzzling rôle of the thymus in lymphocyte production is considered in the light of recent work with tritiated thymidine and irradiation in thymectomized animals.

Ten of the 101 pages of this book are given to the results of cell transfusions after irradiation of animals. The protective effect is mentioned of marrow and spleen cells, but not of thoracic-duct lymphocytes and thymocytes.

This small book is well written and clearly set out with numerous subheadings. There are 10 useful tables, 16 figures and an extensive up-to-date bibliography. It should be read by all hæmatologists and others interested in the lymphocyte and its function.

The Modern Educational Treatment of Deafness: Report on the International Congress held at the University of Manchester, 15th-23rd July, 1958. Edited by Sir Alexander Ewing; 1960. Manchester: Manchester University Press; Carlton: Melbourne University Press. 9¼" × 6", pp. 72 (papers) with illustrations. Price: 64s. 9d.

THE otologist finds it all to easy to slip into the habit of regarding deafness as a defect of the ear. He then may view his own efforts to restore hearing as a contribution out of all proportion to the total problem. Those efforts have, of course, been considerable, especially during the past two or three decades; but he must, if he is truly critical, see areas in which he has made very little contribution to the total progress. Any otologist who fails in this view should read the papers collected under this title.

In terms of human deprivation and suffering, the plight of children with congenital or neonatal deafness, and that

of their parents, presents a tremendous challenge to education and to social workers on many fronts. This challenge has been met by an increasing response, as the psychological and social implications of the disability have been increasingly understood.

The 72 papers collected in this volume represent the material presented at the International Congress on the Modern Educational Treatment of Deafness in the University of Manchester in July, 1958. The convener and director of the Congress was Sir Alexander Ewing, who also makes several important contributions. An introduction and commentary by Lady Ewing to a closed-circuit television session on diagnostic tests of hearing and parent guidance must be one of the last published statements of this distinguished and gracious woman, who will be remembered in Australia for her visit here with her husband in 1950.

The plenary sessions dealt with recent developments in physiology of hearing, acoustics of speech, ætiology, pathology and treatment of deafness in childhood, and many aspects of the educational and social services provided for deaf children in England, the United States of America, Holland, Germany, Soviet Russia, Denmark and France. Sectional sessions embraced a wide range of subjects, such as teaching problems, psychological development, the use of hearing aids, and deaf children with additional handicaps such as cerebral palsy. There is one contribution by an Australian.

Many of the papers describing clinic and educational work are ingenious and stimulating, though some suggest by their superficiality that all the work represented may not be of the same high quality. However, one cannot help but be impressed by the warm humanity and devotion which are evident in the approach of many of the teachers and investigators in this involved and often frustrating field of endeavour.

These papers are very solid reading, but will be richly rewarding in some way or other to all who are concerned with deaf children.

Chronic Cor Pulmonale, Report of an Expert Committee. World Health Organization Technical Report Series No. 231; 1961. Geneva: World Health Organization. 9½" × 6¼", pp. 35. Price: 1s. 9d. (English).

THE attention of the Director-General of the World Health Organization has recently been drawn to the fact that although lung diseases causing pulmonary heart disease are being studied extensively in many parts of the world, there is little reliable information concerning the incidence of important secondary effects on the pulmonary circulation and right ventricle. Furthermore, there has been no agreement among physiologists, pathologists or clinicians as to terminology; hence great difficulties have arisen in communicating findings of mutual interest and importance. In addition, it was held that the wide disparities in the reported incidence of the disease in different areas might be due, in part at least, to inconsistencies in the diagnostic terminology.

As a consequence, an Expert Committee of the World Health Organization was convened in Geneva in October, 1960, with the object of making a unifying statement on chronic cor pulmonale, and the present monograph is the report of this group. The stated objectives of the report are as follows: (i) to define chronic cor pulmonale in terms useful for further discussion; (ii) to provide a tentative classification of diseases which may be the cause of this syndrome; (iii) to describe in broad terms the pathophysiology of cor pulmonale and to establish criteria for diagnosis. The Committee then go on to state that "if these objectives are attained even in part, it is believed that the report will provide a language with which physicians throughout the world can communicate with one another and compare clinical experience and research findings". They have succeeded in attaining their objectives in a remarkably succinct fashion. In the space of 35 pages they deal in order with the definition and classification of chronic cor pulmonale, physiological derangements, clinical recognition, treatment, prevention, and suggestions for research and recommendations.

We do not agree with some of the points raised; but these are minor and do not detract from the value of this report. For example, it is difficult to believe that isolated right ventricular enlargement can be confidently recognized in an X-ray film of the chest. Nor do we agree that right ventricular hypertrophy can be diagnosed on the electrocardiogram on the presence of clockwise rotation, right axis deviation and incomplete right bundle branch block—such evidence is indirect and not diagnostic. Treatment is dealt with in a few lines only; but this is not unreasonable in a publication of this type, which is concerned fundamentally with definition and classification. We can recommend this publication to all those interested in clarifying their ideas on this most confusing subject.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Genetic Perspectives in Disease Resistance and Susceptibility", Volume 91, Art. 3, of the Annals of the New York Academy of Sciences, edited by F. N. Furness; 1961. New York: The Academy. 9" × 6", pp. 595-818, with illustrations. Price not stated.

"Toxoplasmosis: A Bibliography of Literature 1956-September, 1960", compiled by Dorothy Bocker, M.D.; 1960. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service. 10¾" × 8", pp. 15. Price: not stated.

"Cell Heredity: An Analysis of the Mechanisms of Heredity at the Cellular Level", by Ruth Sager and F. J. Ryan; 1961. New York, London: John Wiley & Sons, Inc. 9" × 6", pp. 412, with illustrations. Price not stated.

"The Merck Manual of Diagnosis and Therapy", edited by C. E. Lyght, M.D.; tenth edition; 1961. Philadelphia: Merck Sharp & Dohme Research Laboratories. 6½" × 4", pp. 1908. Price: Regular Edition, U.S.$7.50; De Luxe Edition, U.S.$9.75.

"Brain Mechanisms and Learning: a Symposium Organized by The Council for International Organizations of Medical Sciences Established under the Joint Auspices of UNESCO and WHO", Consulting Editors, A. Fessard, R. W. Gerard and J. Konorski; Editor for the Council, J. F. Delafresnaye, C.I.O.M.S.; 1961. Oxford: Blackwell Scientific Publications. 9" × 5½", pp. 702, with illustrations. Price: 70s.

"British Empire Cancer Campaign: Thirty-Eighth Annual Report Covering the Year 1960. Part II: The Scientific Report of the Researches Undertaken by the Central Organization and its Autonomous Councils in the United Kingdom, and by Some of its Affiliated Organizations Overseas"; 1961. 9¾" × 7¼", pp. 792. Price not stated.

"Medicine and the Navy 1200-1900: Volume III, 1714-1815", by Christopher Lloyd, F.R.Hist.S., and J. L. S. Coulter, F.R.C.S., foreword by Surgeon Vice-Admiral Sir Cyril May, K.B.E., C.B., M.C., F.R.C.S.; 1961. Edinburgh, London: E. & S. Livingstone. 8¾" × 6¼", pp. 402, with illustrations. Price: 50s. (English).

"Some Aspects of Obliterative Vascular Disease of the Lower Limb", by J. A. Gillespie, M.D., Ch.M., F.R.C.S., and D. M. Douglas, Ch.M., F.R.C.S.; 1961. Edinburgh, London: E. & S. Livingstone. 9¾" × 7", pp. 136, with illustrations. Price: 30s. (English).

"A Manual of Psychiatry", by K. R. Stallworthy, M.B., Ch.B.; fifth edition; 1961. Christchurch: N. M. Peryer Limited. 7¼" × 4¾", pp. 386. Price: 30s. (New Zealand).

"A Radiographic Index", by Myer Goldman, M.B., Ch.B., D.M.R.D., Ronald S. Miller, M.R.C.S., L.R.C.P., D.M.R.D., and David Cope, F.S.R.; 1961. Bristol: John Wright & Sons Ltd. 6¼" × 4", pp. 88. Price: 13s. 6d. (English).

"Comparative Epidemiology of the Mental Disorders", edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D.; 1961. New York, London: Grune & Stratton, Inc. 8½" × 5½", pp. 290, with illustrations. Price: $9.75.

"Current Psychiatric Therapies, An Annual Publication", Volume I, edited by J. H. Masserman, M.D.; 1961. New York, London: Grune & Stratton. 9" × 6", pp. 246. Price: $7.50.

"Recognizing the Depressed Patient, with Essentials of Management and Treatment", by Frank J. Ayd, Jr, M.D.; 1961. New York, London: Grune & Stratton, Inc. 9" × 6", pp. 138. Price: $3.75.

CIBA Lectures in Microbial Biochemistry, "Microbial Cell Walls", by M. R. J. Salton; 1960. New York, London: John Wiley & Sons, Inc. 7¼" × 5", pp. 94 with illustrations. Price: $3.50.

"Automatic Process Monitoring", Volume 91, Art. 4, of the Annals of the New York Academy of Sciences, edited by F. N. Furness; 1961. New York: The Academy. 9" × 6", pp. 819-935 with illustrations. Price not stated.

The Medical Journal of Australia

SATURDAY, OCTOBER 14, 1961.

ALL IS NOT WHAT IT SEEMS.

It is not so very long ago since our physician forefathers had no help in arriving at a diagnosis, other than their capacity to take a careful history and to make an equally painstaking physical examination. Our elders would still have us believe that, by the patient application of their skill in each, they achieved an accuracy in diagnosis which we, in our generation, have failed to match. We suspect that this is far from being the truth and, to support our argument, we cite diseases of the gastro-intestinal tract in which we have, by the development of special investigations, achieved a degree of exactness in diagnosis unthought of 30 years ago.

There has, for example, been striking improvement in radiological technique. Equipment and viewing conditions are better, positioning is made easier, and film changing is quicker and more precise. Radiation risk is less and the examination correspondingly more complete. It is little wonder, then, that we can now detect conditions which in earlier days escaped our attention. A good example of this is hiatus hernia. A young surgeon preparing for his fellowship 20 years ago was expected to be familiar only with the writings of Basil Hume of "Bart's" and of Stuart Harrington of the Mayo Clinic. Diaphragmatic hernia, as it was then, was a rare bird. Since the end of World War II, however, a voluminous literature has accumulated on this condition, and it features prominently nowadays in every undergraduate text. Improvements in our diagnostic methods have made us very keenly aware of the troubles which this condition can occasion, and we have a reasonably complete understanding of their correction. At the same time we have come to realize that hiatus hernia is, in our adult community, very common and does not always cause trouble, so that we are likely, not too infrequently, to stumble across it when we are really looking for other things.

Now there is another disease process in our community which is exceedingly common. The records of the Royal Melbourne Hospital (R. A. Joske *et alii*[1]) tell us that we can expect at autopsy to find stones in one out of every six gall-bladders, and J. B. Cleland's figures from Adelaide are little different.[2] Gall-stones in the files of our X-ray departments are two a penny. They disturb our attention when we are looking for a fracture in the lumbar part of the spine. They confuse the issue when we are searching for a duodenal ulcer. Stones blocking the cystic duct cause biliary colic and call for the doctor in the middle of the night: stones filling a thick-walled and inflamed gall-bladder induce flatulent dyspepsia and a visit to the radiologist. It is, however, important to remember that many stones are silent—so silent that there is no visit to the doctor, no call for a prescription, no restriction of diet and an excellent digestion. Our patient and his stones are living together in apparent harmony, and many would be inclined to leave them both in peace.

With the knowledge that hiatus hernia and gall-stones are, in our adult community, common conditions, we would expect, with a frequency which could no doubt be determined, to find the two conditions occurring together, and this, experience (and often bitter experience) has proved to be the case. Their coexistence in any patient would be of little consequence to us as doctors, however distressing to our patient, if unhappily they did not both give rise to similar symptoms. Not surprisingly we indict the first that we discover. The gall-bladder with its silent stones is sacrificed, but the symptoms persist until later we find and repair an hiatus hernia. Nor is our patient any better off if we first cobble a symptomless hernia before turning our attention to the real source of trouble, the gall-bladder full of stones. If we tackle both across the abdomen, we may still be able to retrieve our mistake and save our patient's discomfort (and his pocket). Our thoracic surgical colleague, proud that his brethren have given us a more complete understanding of the anatomical abnormality and of its proper correction, yet shy to trespass too far beyond the arbitrary lower boundary of his domain, commonly makes his approach to the repair of an hiatus hernia across the chest. It would be surprising if he did not sometimes share with the general surgeon the discomforture of an incorrect diagnosis.

Matters are, however, even worse than this, for the innocent gall-bladder or hiatus hernia may be the whipping boy for other and more serious disorders. Cancer of the stomach will pass unnoticed if the hand cannot reach beyond the diaphragm, and cancer of the caecum may still escape the attention of the surgeon intent on repairing an inaccessible hiatus from below. We are particularly likely to make mistakes when, during the course of an exhaustive but fruitless investigation to determine the source of an episode of gastro-intestinal bleeding, we light on an hiatus hernia and, with something of the unreasoning eagerness of a drowning man clutching at a straw, mark it down as the cause, when subsequent events make it perfectly obvious that it was no more than an incidental finding, completely irrelevant to the recent bleeding. The same kind of argument is applicable in relation to diverticulosis or diverticulitis, for this is yet another disorder of the gastro-intestinal tract which is both not uncommon and silent (I. P. Todd[3]). Equally, it can cause symptoms of obstruction which may simulate closely cancer of the colon. Here again it is easy enough to fall into the trap when, on the basis of a good clinical history, we have made a confident diagnosis of cancer of the colon, which

[1] Med. J. Aust., 1954, 2: 473 (September 18).
[2] Med. J. Aust., 1953, 2: 488 (September 26).
[3] *Ann. roy. Coll. Surg. Engl.*, 1955, 16: 118.

our radiologist has failed to confirm, we immediately seize hold of his alternative of diverticulosis and tragically overlook an early carcinoma hidden away in a barium shadow. On the basis of his report we may, uncritically or unthinkingly, set aside our clinical judgement, which was no doubt determined on firmer and more illuminating evidence than that picked up by the radiologist, working, literally, in the dark. The mistake once made is tragically perpetuated, as we continue the expectant policy to which our innocent diagnosis has committed us. It almost seems that we are now too clever in ferreting out these silent abdominal conditions. Unfortunately it is true that their correction is often thought to be so easy that we tend to give the problem less thought and care than circumstances demand. We suspect that many gall-bladders each year are wrongly sacrificed to atone for the misdemeanours of others, and that in the process much harm can be done which may be the genesis of additional disabling symptoms. It may well be that there is, after all, something in the assertion of our senior colleague. His implied criticism, however, is valid not when it is directed against our diagnostic methods or even against our use of them, but only when he complains of apparent lack of judgement. What is needed is not so much a little less science as a lot more care and a lot more discernment. The master who hurries into the school yard to investigate the cause of a broken window, is tempted to apprehend the first young rogue with a stone in his hand he sets his eye on, but from bitter experience he has come to recognize that a schoolboy with a missile in his hand is all too common a phenomenon, and that, as likely as not, the real culprit will be trying his best to hide round the corner. Like him, we must make quite certain that we bring the real culprit to justice, and first time, too!

Comments and Abstracts.

RESULTS AT A CANCER DETECTION CLINIC.

SINCE the idea of special cancer detection clinics was first developed in North America, and since experience of this kind of work is still predominantly American, the results obtained at the American clinics are of prime importance for those interested in the development of such clinics elsewhere. The Cancer Detection Center of the University of Minnesota Hospitals has been in operation since early in 1948, and C. B. Jenson, D. B. Shahon and O. H. Wangensteen[1] have now summarized the first eleven years' experience of this clinic in an attempt to evaluate the results of annual examinations in the detection of cancer. The Minnesota Cancer Detection Center provides for the examination of a select group of patients. The prerequisites for enrolment are (i) legal residence in Minnesota and (ii) lack of symptoms that would ordinarily require a physician's services. In addition, enrolment is restricted to those aged 45 years or over in the case of women, and 50 years or over in the case of men, as 90% of all malignant conditions occur in these age groups. Before they are examined all subjects must agree that they will return to their family doctor to ascertain the results of their examinations, and that they will continue to return for the same examinations at yearly intervals. Every patient admitted to the clinic is subjected to the following procedures: analysis of gastric secretions, procto-sigmoidoscopy, pelvic examination with Papanicolaou smears in the case of women, general physical examination, complete blood count, analysis of urine, testing of stool for occult blood, and a chest skiagram (14 × 17 in. film). Additional special procedures are performed when indicated.

The material studied included all histologically proved cases of cancer of the breast, stomach, large bowel, prostate, ovary and uterus discovered during the eleven years under review. During this period, 4367 men and 4756 women underwent a total of 33,224 examinations, and 163 cases of cancer of the organs listed were diagnosed as a direct result of examination at the Cancer Detection Center. In addition, 42 cases of such cancers were identified by studies initiated by outside practitioners in the intervals between annual examinations, but these were not included in the general analysis. Malignant conditions discovered in organs other than those listed were too few to yield useful information.

As so often happens in this kind of study, in spite of the very large number of patients examined, the authors are up against the difficulty that the number of cases of any one type of cancer is too small to yield very much information. However, some interesting points emerge. Nearly two-thirds of the cancers found were discovered at examinations subsequent to the first (this includes the 42 cases discovered during the intervals between annual examinations). The proportion of malignant lesions which were completely asymptomatic when discovered varied greatly from one organ to another, as would be expected; but when cancers of the breast, ovary, cervix and rectum were compared with those of the prostate, stomach, colon and endometrium, it was found that 73% of the former group were asymptomatic when first diagnosed as compared with only 32% of the latter group. It appeared to make little difference whether the tumour was diagnosed at the first visit or at a subsequent examination. In 15 of the 21 cases of breast cancer discovered subsequently to the first examination, the lump had been unnoticed by the patient, in spite of the fact that all women patients had been instructed in self-examination of the breasts. Of the 18 women whose breast cancers were detected before they themselves had noticed anything amiss, all were alive and well when the report was written. Nine cases of carcinoma of the cervix were discovered at first examination, but, rather unexpectedly, only four were discovered at subsequent examinations.

On the experience of their clinic, Jenson and his colleagues conclude that an annual examination in a cancer detection centre provides a method that materially reduces the mortality of breast cancer; cancers identified at subsequent annual examinations are likely to be less advanced and more amenable to curative treatment than those discovered in ordinary practice. They also note a marked decrease in the incidence of cancer of the rectum in patients seen at yearly intervals, and suggest that this may be due to the removal of precancerous lesions. Finally, they point out that cancer detection centres play an important rôle not only in the detection of cancer during the asymptomatic phase, but also in achieving a better understanding of the pathogenesis of malignant disease.

[1] *J. Amer. med. Ass.*, 1960, 174: 1783 (December 3).

ACRODERMATITIS ENTEROPATHICA.

THERE are times when collection of new and rare disease entities appears a somewhat academic pastime. However, the reward can be great when the correct delimitation of a rare condition leads to the discovery of a specific cure which may completely alter the outlook for the patient. This appears to be the case with acrodermatitis enteropathica, a condition which was first clearly defined in 1942 by two Norwegian workers, N. Danbolt and K. Closs,[1] and which is characterized by alopecia, skin lesions of a characteristic pattern and intestinal symptoms

[1] *Acta derm.-venereol. (Stockh.)*, 1942, 23: 127.

suggestive of fat malabsorption. Since then about 30 further cases have been reported in detail. Eleven years after the condition was first described it was discovered, almost accidentally, that the condition responded dramatically to "Diodoquin" (diodohydroxy quinoline) given by mouth. This discovery was published in a paper by C. J. Dillaha and colleagues,[2] but the suggestion to use "Diodoquin" had been passed to them by E. H. Schlomovitz, who had used it successfully in a similar case which had been diagnosed as one of systemic moniliasis. Previous to this discovery no treatment had been effective. The disease was subject to periods of remissions and exacerbations, and severely affected patients usually died in childhood. In breast-fed babies the disease commonly appears about the time of weaning, or when other foods are introduced into the diet. In bottle-fed babies it may appear much earlier. The disease is frequently misdiagnosed, most often as systemic moniliasis, an error made all the easier by the fact that the lesions often become secondarily infected with *Candida albicans*. However the condition is not improved by the administration of nystatin, and there are many important distinctions between the two conditions. Another condition with which it has been confused is epidermolysis bullosa.

R. Kelly and C. M. Anderson[3] have recently described a case in an eight-year-old boy which they believe to be the first fully reported in Australia, though in the discussion which followed their paper two other dermatologists referred to atypical examples of the condition which they had encountered. In view of the similarity of the intestinal symptoms to cœliac disease, Kelly and Anderson first tried the effect of a gluten-free diet before initiating "Diodoquin" therapy. The patient developed an exacerbation of his condition before the trial period was over, but improvement set in by the end of two weeks on "Diodoquin", and by the end of six weeks the skin was clear, the hair was growing again and the patient was gaining weight. Since then the child has remained well, though it has been necessary to increase the dose of "Diodoquin" from 1500 mg. to 1800 mg. daily during intercurrent infections. Fortunately, large doses of "Diodoquin" for long periods appear to be well tolerated, as it appears to be necessary to continue the treatment at least till puberty is reached. Kelly and Anderson comment that acrodermatitis enteropathica is "a mysterious disease with an equally mysterious treatment, the symptoms and signs responding completely to a poorly absorbed drug, diodoquine".

Elsewhere, D. Bloom[4] has reviewed the recent literature on the subject in the light of studies on another patient whom he has followed since 1953. He has also obtained information about the subsequent course of the disease in several patients previously described by other writers. It is now widely accepted that acrodermatitis enteropathica is an hereditary, or at least a familial, condition, since in a considerable proportion of the described cases, more than one case has occurred in the same sibship. Like Kelly and Anderson, Bloom suggests that it may find a place among that growing assemblage of conditions described as inborn errors of metabolism, though the specific defect is as yet unknown. Several workers have found that there is a relative deficiency of trypsin in the duodenal fluid in these cases, though in Kelly and Anderson's case this defect was not marked and the malabsorption symptoms were only mild. Bloom has studied this aspect of the condition in some detail, and found that in his case pancreatic secretion appeared to be normal and that the malabsorption is not due to a defect in the intestinal mucosa; he concludes that the basic pathogenetic factor in acrodermatitis enteropathica is faulty digestion due to an unknown factor other than pancreatic enzyme insufficiency. In this he supports the concept that the skin manifestations are the result of nutritional disturbance caused by malabsorption from the gastro-intestinal tract. Whether or not this interpretation is correct, the pictures of the four patients in the four papers discussed here present a remarkable uniform facies, with the head bald, crusting around the mouth, and symmetrical skin lesions in the groins, around the elbows and knees, and on the hands and feet.[5] This appears to put this condition in the category of diseases which, in their fully developed form, it is possible to recognize at sight.

[2] *J. Amer. med. Ass.*, 1953, 152:509 (June 6).
[3] *Aust. J. Derm.*, 1960, 5:219 (December).
[4] *N.Y. State J. Med.*, 1960, 60:3609 (November).

PROGRESS AGAINST YAWS.

THE annual report of the Regional Director of WHO in the Western Pacific notes conspicuous progress towards the eradication of yaws, traditionally a cause of widespread morbidity in many communities throughout this region. It is stated that a few years ago 15% of the population was affected in some island territories, where it was primarily a disease of children living under unhygienic conditions. In most cases the disease went untreated, and in its later stages it was often the cause of crippling and mutilating lesions. When it was discovered that the yaws *Treponema*, which is highly sensitive to penicillin, could be eradicated in early cases by a single injection of a long-acting preparation of this antibiotic, the way was open for mass treatment campaigns against the disease. A world-wide campaign was launched by WHO about 10 years ago, and in 1954 this was extended to the South Pacific, beginning first in Fiji. As national teams were trained, the campaign proceeded in an "island-hopping" fashion to Western Samoa, the Solomon Islands, the Gilbert and Ellice Islands and the New Hebrides—together these islands have a population of about half a million, living in an area of about a million square miles. As an example of the progress made, in the Solomon Islands over 97% of the 110,000 population were seen during the initial mass treatment survey in 1956. At that time 14·7% of the population suffered from yaws. During a second survey in 1959 the incidence of infectious yaws was found to be only 0·13%. Much larger campaigns, as far as numbers are concerned, have also been carried out in Indonesia, Thailand and elsewhere. However, in some parts of the Western Pacific Region such as Cambodia, Malaya, Tonga and Portuguese Timor, there are yaws-endemic areas still to be tackled, though these are mostly areas in which the original problem was less serious. Also, in a few countries there are still remote areas which have not yet been reached by modern medicine in any form.

Over a considerable part of the region, therefore, yaws has ceased to be a major public health problem, and the few remaining cases must be the responsibility of the established health services. Total eradication is a fine goal, but in practice the last case of any disease is very difficult to track down, and only patient perseverance and continuing improvement in standards of general hygiene and medical care will consolidate the ground so spectacularly gained. In the case of yaws a further proviso must be added. As the high incidence of yaws in the past may have conferred some degree of immunity against syphilis, health authorities should beware lest the disappearance of yaws prepares the way for the spread of venereal syphilis.

SHORTER ABSTRACTS.

PHYSICAL MEDICINE AND REHABILITATION.

UNIFORMITY IN CLINICAL ELECTROMYOGRAPHY. K. H. Haase, *Arch. phys. Med.*, Jannary, 1961.

THE author outlines a standard routine and procedure to establish uniformity in clinical electromyography. He states that the electromyogram is as essential to the physiatrist as the electrocardiogram is to the cardiologist. The method evolved by the author as a result of more than 8000 examina-

[5] A photograph of Kelly and Anderson's patient appears on page 622 of this issue, with a synopsis of his case history.

tions is presented. Electromyography is a dynamic examination, which should be made only by a trained physician. In the interpretation of the results, the primary criterion for denervation should be the fibrillation of denervation voltage. The positive denervation sharp wave should also be considered as one of the criteria of denervation. The author also describes and explains myotonic voltages and dystrophic activity. He states that the written electromyographic report should include the muscles examined with their peripheral nerve and root innervation. There should be a report of abnormality found in each muscle examined. If evidence of denervation is present, the level of the lesion should be indicated. There should be a statement as to whether the lesion is partial or complete. When indicated, a statement should be made as to the prognosis and as to the necessity for serial examinations. The author emphasizes that electromyography is not the ultimate in electrodiagnosis; a standard routine should also include conduction velocity and quantitative excitability studies. Standardization of technique and procedure will hasten progress in the understanding of neuro-muscular function and disorders through future valid correlative clinical research.

CHRONIC SEQUELÆ OF POLIOMYELITIS. C. Vallbona and W. A. Spencer, *Arch. phys. Med.*, February, 1961.

THE authors state that invasion of the central nervous system by the viruses of poliomyelitis has direct and indirect effects on other systems of the organism. This may produce multiple clinical syndromes at different stages of the chronic phase of the disease. Some of these syndromes are the cause of early death in many cases. In others, the depletion of physiological reserves appears to lead to premature aging of some physiological systems. Experience acquired in the last ten years in poliomyelitis respiratory and rehabilitation centres has led to identification and description of several syndromes that complicate the course of chronic poliomyelitis. A systematic classification of these chronic sequelæ is presented, and its relative incidence in the three major "anatomical" forms of poliomyelitis is indicated. The authors state that special emphasis should be placed on the avoidance of injudicious scheduling of physical activities and treatments for patients with residual paralysis of the respiratory muscles. Early diagnosis of these sequelæ and their immediate treatment are possible only by means of periodical examinations of poliomyelitis patients. The most frequent signs and symptoms are reviewed, and methods of evaluation are suggested according to the experience gained from observations made in the Southwestern Poliomyelitis Respiratory and Rehabilitation Centre on more than 1500 patients with poliomyelitis.

DISUSE OSTEOPOROSIS. A. S. Abrahamson and E. F. Delagi, *Arch. phys. Med.*, March, 1961.

THE authors discuss the influence of weight-bearing and muscle contraction on disuse osteoporosis. They state that disuse is only one of many causes of osteoporosis, by reason of the reduction of "stress and strain" on bone. Frequently several causes operate in the same patient. There is no unequivocal evidence that osteoporosis is reversible; therefore the therapeutic effort should be directed towards prevention. Disuse osteoporosis and its resultant metabolic losses are self-limited. Losses are greater with greater immobilization. Treatment based on other than the primary cause can be expected to have only limited effectiveness. Muscle action is the most effective stress upon bone in the prevention of disuse osteoporosis. Weight-bearing is much less effective than muscle action, but is probably not entirely ineffective in limiting osteoporosis. The muscle action of spasticity is useful in that it probably preserves bone. Anabolic agents can partially limit disuse osteoporosis. Treatment should be applied early. The authors consider that disuse osteoporosis would be a rewarding field of investigation.

SPECIAL APPLIANCES FOR THE DISABLED. R. H. Nyquist, *Arch. phys. Med.*, 1961, 42: 164-166 (March).

THE author describes a special appliance for the disabled upper extremity of a quadriplegic patient with a lesion at the fourth, fifth and sixth cervical vertebræ and with about 55% to 60% function at the shoulder and elbow. The brace is partially a Georgia Warm Springs Foundation type with the addition of a "C"-bar and an opponens bar. The adaptive equipment is fastened to the brace at two different points by means of a double keyhole type of fastening slot. The spoon for feeding is fashioned after a scoop shovel and is fastened to the brace by a swivel joint which allows gravity to keep the spoon level on the way from the plate to the mouth, decreasing spillage from the spoon. A "stop-bar" is arranged so that pressure can be afforded against this bar, the spoon being held so that it is more stable when food is scooped from the plate on to the spoon. The plate is equipped with a metal band to hold the food on the plate against the pressure of the edge of the spoon. This metal plate guard is held to the plate with a metal clip in a stronger manner than with plastic. Two attachments for writing include a "sliding bar" and a pencil holder. A metal holder is provided for an electric razor, and this holder can be swivelled to allow better positioning on various parts of the beard. An attachment for the tooth brush allows swiveling and various positions for brushing the teeth on both sides of the mouth.

MOTOR NERVE CONDUCTION VELOCITY STUDIES IN "IDIOPATHIC" POLYNEURITIS. D. Cerra and E. W. Johnson, *Arch. phys. Med.*, 1961, 42: 159-163 (March).

THE authors have carried out periodic motor nerve conduction velocity and electromyographic studies on 25 patients suffering from "idiopathic" polyneuritis, over a period of three years. In all cases, reduced conduction velocity was helpful in the diagnosis. The decreased velocity preceded the electromyographic changes by one to two weeks; velocity gradually increased in parallel with clinical recovery, although, in several long-drawn-out cases, it did not return to normal values. Frequently temporal dispersion of the muscle action potential was the first indication of reduced velocity. The authors present supporting clinical data, biopsy studies and a brief review of the literature.

THE APPLICATION OF PSYCHOMETRICS IN THE VOCATIONAL EVALUATION OF THE ADULT SEVERELY DISABLED. D. Spangler *et alii*, *Arch. phys. Med.*, 1961, 42: 180-184 (March).

THE authors discuss the application of psychometrics in the vocational evaluation of the adult severely disabled. They state that by these tests are obtained useful data which aid the comprehensive rehabilitation process. They make a distinction between evaluation for selection and evaluation for guidance. The latter point of view seems better in relation to rehabilitation. The authors discuss two approaches —the need for taking measurements over time, and the relationship of the use of tests to local conditions. The authors note some trends in testing the disabled, and state that, although the Wechsler tests still enjoy wide application for evaluating intellectual status, there has been an increasing use of measures which minimize the response demands placed upon the disabled subject. The projective tests and their modifications have become the preferred methods of personality assessment, in spite of the frequent use of the Minnesota Multiphasic Personality Inventory. In the appraisal of certain special abilities, performance tests involving manipulative activities appear to be of considerable value. The authors finally point out some implications for research.

NEUROLOGY.

CEREBRAL ARTERIAL THROMBOSIS IN CHILDREN. H. S. Wisoff and A. B. Rothballer, *Arch. Neurol.*, 1961, 4: 258-267 (March).

THE authors review the literature and describe two cases of cerebral arterial thrombosis in apparently healthy children. The diagnosis in their two cases was made by angiography. One child died of massive encephalomalacia and was demonstrated to have widespread degenerative disease of the media and intima of both systemic and cerebral arteries. The authors have studied two familial cases of the disorder from the clinical, histological and chemical points of view.

STUDIES ON HEADACHE. Walter A. Camp and Harold G. Wolff, *Arch. Neurol.*, 1961, 4: 475-485 (May).

THE authors discuss the electroencephalographic abnormalities in patients with vascular headache of the migraine type. A large number of patients with the complaint of headache were studied by means of electroencephalography, the distribution of normal records being approximately the same as that found in a headache-free population. Among

a group of patients with vascular headaches of the migraine type, the incidence of abnormal electroencephalograms increased to twice that found in healthy subjects. The electroencephalographic abnormalities in patients with vascular headaches fell into two categories: (i) paroxysmal or diffuse 4 to 7 c.p.s. activity between attacks; (ii) focal abnormalities, (*a*) present only during an attack, (*b*) present in the headache-free period, probably due to cerebral infarction.

Intracranial Bleeding in Hæmophilia. A. Silverstein, *Arch. Neurol.*, 1960, 3: 141-157 (August).

The author discusses intracranial bleeding in hæmophilia. He found that it occurred in some 5% of the hæmophiliacs admitted to the Mount Sinai Hospital, New York. He analysed 31 proved cases, and found that intracranial bleeding occurred mostly in young hæmophiliacs; previous head trauma was a significant ætiological factor; convulsions occurred in more than half the patients, and intracranial bleeding not uncommonly recurred. There was a greater tendency for intracranial bleeding to occur in patients with antihæmophilic globulin deficiency. The author states that while lumbar puncture can be safely performed, surgical intervention, with the possible exception of craniotomy for bleeding confined to the subdural or epidural spaces, is unwise. Intracranial bleeding in hæmophiliacs frequently occurs subdurally, epidurally or intracerebrally. Subarachnoid bleeding is the least common, but has the best prognosis. He found the overall mortality from intracranial bleeding to be greater than 70%.

Psychogenic Regional Pain alias Hysterical Pain. A. Walters, *Brain*, 1961, 85: 1-18 (March).

The author discusses 430 cases in which this type of pain occurred. The sites in the body where the pain occurred in these cases did not conform to the sites of pain with local physical lesions, or to the areas of referred pain. The pain had a more regional distribution. He concludes that we do not know how these regional pains and regional patterns of injury are produced. The factors of stress seem to set the stage, and a precipitating stimulus which carries noxious meaning evokes the response. He holds that the current concepts of conversion and conversion hysteria do not account for all types of pain described. In some the pain and behaviour of injury seem to be direct emotional expressions of personal injury; in others the efficient cause cannot be elicited. He holds that psychogenic regional pain is a more useful term than hysterical pain as an accurate designation for these pains.

Quadriceps Myopathy Occurring in Middle Age. J. W. A. Turner and K. W. G. Heathfield, *J. Neurol. Neurosurg. Psychiat.*, 1961, 24: 18-21 (February).

The authors review two cases of myopathy limited to the quadriceps. One case reported in 1939 has been under investigation for 20 years, during which time there has been very slow spread of the muscle involvement. A second case of similar localized wasting and weakness of the quadriceps and marked changes on muscle biopsy is reported. It seems probable that these patients are suffering from chronic polymyositis rather than from progressive muscular dystrophy.

Occlusion of Intracranial Venous Structures. H. Lemmi and S. C. Little, *Arch. Neurol.*, 1960, 3: 252-266 (September).

The authors consider the clinical and electroencephalographic findings of occlusion of intracranial venous structures. This was a study of 13 patients diagnosed as having occlusion of the intracranial vascular structures. The patients with thrombosis of superficial cerebral veins usually had focal convulsions and cortical neurological deficits, which were either transient or permanent. If seizures recurred months or years later, they often appeared to originate in the Sylvian area. Electroencephalographic studies in both acute and chronic stages correlated well with the acute and chronic encephalopathy. In some cases thrombosis of a superficial cortical vein preceded thrombosis of the superior longitudinal sinus. The electroencephalographic changes in thrombosis of the superior longitudinal sinus usually consisted of pronounced slowing in the prefrontal areas. This might be followed by two-per-second wave-and-spike patterns if chronic encephalopathy resulted. The electroencephalographic patterns in a single patient presumed to have thrombosis of both the superior longitudinal sinus and the deep cerebral veins were not essentially different from those found in thrombosis of the superior longitudinal sinus alone. The authors conclude that the character and distribution of the electroencephalographic abnormality in thrombosis of the superior longitudinal sinus are sufficiently constant to be of considerable diagnostic value, but the electroencephalographic changes in thrombosis of superficial cortical veins and other venous structures are much less characteristic, and may be of little or no diagnostic help.

Cerebrovascular Accidents in Patients Receiving Anticoagulant Drugs. C. E. Wells and D. Urrea, *Arch. Neurol.*, 1960, 3: 553-558 (November).

The authors have studied the clinical course in 23 patients who had 26 vascular accidents while receiving long-term anticoagulant therapy. Fourteen of these patients had primary intracranial hæmorrhages (including five subdural hæmatomas), nine had cerebral emboli and three had cerebral thromboses. Nine of the episodes ended in death, but the overall mortality rate was no greater than might have been expected in a group of untreated patients. The high incidence of subdural hæmatomas suggests that when coagulability is reduced by use of anticoagulant drugs, relatively slight head trauma may lead to a subdural hæmatoma. Six of the nine deaths occurred in hypertensive patients, in five of whom intracranial hæmorrhage took place. Thus with anticoagulants the danger of cerebral vascular accident appears much greater in the hypertensive than in the normotensive patient.

Quantitation of Muscle Tone in Normals and in Parkinsonism. J. Brumlik and B. Boshes, *Arch. Neurol.*, 1161, 4: 399-406 (April).

The authors have studied the muscle tone in 30 normal subjects and in 30 subjects with Parkinsonism, by the use of an electromechanical method with carefully controlled criteria. They conclude that their study indicates that muscle tone in the human can be quantified, and that these measurements can be utilized in determining subsequent changes in the course of the disease, the effects of medication and surgical procedures.

Princeton Conference on Cerebrovascular Disease. F. Plum, *Arch. Neurol.*, 1961, 4: 471-474 (May).

The author gives a brief summary of the Princeton Conference on Cerebrovascular Disease. The emphasis was placed on diagnostic techniques and recent developments in treating three major groups of cerebrovascular disease—incipient or impending strokes, progressive strokes and completed strokes. Sixty-eight *per centum* of patients with severe carotid stenosis have a 5 to 10 gramme reduction in retinal artery pressure in the ipsilateral eye. Arm-retina circulation times, measured with fluorescent dye, are predictably delayed on the side of carotid occlusion. Denny-Brown suggested that episodic hypotension or reduction in cardiac output might frequently be the factor that converted an asymptomatic arterial lesion into the cause of a stroke. Fisher summarized a controlled study using anticoagulants for transient ischæmic attacks. There were 570 recurrent attacks in the control group as compared with 20 recurrences among the treated. McDevitt emphasized the accelerated rate of thrombo-embolic attacks which follow during the month after withdrawal of anticoagulants. The surgical approach was discussed. It was stated that many patients with transient ischæmic attacks having partially obstructing extracranial arterial lesions were completely freed of attacks after endarterectomy, while the mortality or serious morbidity from the procedure was reduced below 10%. Meyer summarized experience in acute stroke using streptokinase-activated fibrinolysin and plasmin combined with anticoagulants; he considered that it was too early to assess fully their potential value. A New York group, using anticoagulants to treat patients with completed stroke, observed a significant reduction of recurrent thrombo-embolism in treated subjects as opposed to untreated controls; on the other hand, a Los Angeles study noted only a modest reduction of thromboembolism among treated patients, but a higher death rate than was observed among controls.

Medical Societies.

AUSTRALIAN PÆDIATRIC ASSOCIATION.

THE annual meeting of the Australian Pædiatric Association was held at Canberra on April 21 to 24, 1961, DR. R. H. CRISP, the President, in the chair.

Election of Office-Bearers.

The following office-bearers were elected for the year 1961-1962:

President: Mr. J. Steigrad.

Honorary Secretary: Dr. J. M. Alexander.

Honorary Treasurer: Dr. D. L. Dey.

State Representatives: Dr. V. Collins (Victoria), Dr. T. R. Biggs (Queensland), Dr. R. Wall (Tasmania), Dr. D. G. McKay (South Australia), Dr. R. H. Crisp (Western Australia).

Flying Doctor "Locum".

DR. DOUGLAS GALBRAITH (Melbourne) read a paper entitled "Flying Doctor Locum" (see page 613).

DR. ELIZABETH GIBSON (Perth) commented that she had flown around with infant welfare sisters who saw all the children in north-west Western Australia. The infant welfare department had a correspondence service with headquarters in Perth, which served patients north of the line joining Broome and Kalgoorlie.

DR. J. STEIGRAD (Sydney) commented from the chair on the happy choice of topic of the opening paper as it gave visitors an insight to the Australian outback.

Cine-Tele-Fluorography in Pædiatrics.

DR. H. G. HILLER (Melbourne) read a paper entitled "Cine-Tele-Fluorography in Pædiatrics". He said that the introduction of image intensifiers to radiology had considerably improved the interpretation of radiological problems in pædiatric fluoroscopic procedures. The principle of accelerating a beam of photo-electrons across a vacuum to produce a thousand times increase in the brilliance of the emergent light had allowed a great reduction in radiographic factors used during screening. This had in turn greatly reduced the patient radiation dosage and had allowed the use of normal lighting in the screening room. However, one big disadvantage was the restriction of viewing to one person, and for this reason some two years before experiments had been carried out at the Royal Children's Hospital, Melbourne, on the problem of coupling closed-circuit television to the image intensifier, so that any number of doctors could view the fluoroscopic examination on a television monitor. The results of these experiments had been extremely satisfactory and for the previous two years about 99% of all fluoroscopies at the Royal Children's Hospital had been done with television.

Over that period further investigations had been carried out to try to devise a means by which a permanent "cine" record of any screening could be obtained through the television-image intensifier system by filming the face of a television monitor. After many setbacks, due mainly to stroboscopic problems, a method of recording on movie film had been perfected and called cine-tele-fluoroscopy.

The equipment incorporated two cameras, both driven by a synchronous motor and both geared to run at the same speed as the television camera. The top camera was used as a viewing camera only to make sure that the motor drive had been started in the correct phase, which in turn made sure that no "strobe" line was visible. The lower camera held the film, and it was started only after a preliminary viewing through the upper camera. Great care had to be taken to guarantee that the lower camera would start and stop with its shutter in the same position, otherwise it was liable to run out of phase with its partner. If this occurred then strobe could appear on the film and so ruin the result.

The advantages of cine-tele-fluorography over cinefluorography were that there was no increased radiation danger to the patient, and the filming could take place without interrupting the fluoroscopy. In fact, it was done in another room, by means of a second television monitor. The main disadvantage was the poorer detail visible in comparison with conventiontal cinefluoroscopy and inherent in any television chain. The film strips obtained might be up to 50 feet in length and could be used in consultation with the referring pædiatrician to demonstrate points not adequately shown on spot films, or to show abnormal motion, as in pharyngeal or œsophageal incoordination. They might also be used to compare the results of treatment in conditions such as corrosive œsophageal stricture to assess the degree of stricture after the passage of bougies. In both student and post-graduate teaching they could be of help in demonstrating such things as the actual mechanism of infant sucking or, at a more advanced level, in showing the problems that might be encountered during cardiac catheterization. Finally the use of cine-tele-fluorography in research projects might well be one of the most important applications of the procedure.

A film showing some examples of the use of this system of cine-tele-fluorography was shown separately.

DR. GEORGE WESTLAKE (Melbourne) confirmed the advantages of such work, especially in planning treatment of cardiac patients.

DR. D. H. COHEN (Sydney) said that the more clearly defined pictures of the usual methods of cinefluorography seemed preferable and asked why there was a difference in the radiation dosage between the two methods.

In reply, Dr. Hiller said that to take a cinefluorogram through the image intensifier necessitated boosting the dosage many times. In the case of cine-tele-fluorography no alteration in radiation was necessary, but there was some loss of definition, which was important only when fine detail was required.

Imperforate Rectum.

DR. E. DURHAM SMITH (Melbourne) read a paper entitled "The Association of Imperforate Rectum with Sacral Agenesis, and the Assessment of Rectal Continence".[1]

Dr. Smith said that rectal continence after rectoplasty for imperforate rectum depended primarily on correct innervation and action of the pubo-rectalis muscle. Stephens (1953) had shown that the other sphincter components generally lacked development. It was therefore of prime importance to assess the innervation of the levator ani before surgery, for if its sacral nerve supply was defective, rectoplasty would be followed by incontinence. One such lesion responsible for defective sacral innervation was agenesis of the sacrum.

Dr. Smith referred to a survey of 89 patients with imperforate anus and rectum; he said that out of 40 patients with high rectal anomalies 22 patients had possessed an abnormal sacrum, whereas out of 49 patients with low anal anomalies only four had possessed such a sacrum. The type of anomaly of the sacrum had varied from total agenesis to minor degrees of hemi-sacrum.

Dr. Smith then referred to a previous paper of his own in which it had been stated that a study of 18 surviving patients with sacral anomalies had suggested that there was strong clinical, urographic, and electromanometric evidence that 17 of those patients lacked urinary and fæcal control. Further, four of six autopsy dissections had revealed that the sacral nerve roots were deficient over limits corresponding to the bony defects. In the severer forms of sacral agenesis, therefore, there was a high probability that the sphincters and, in particular, the levator ani might lack their nerve supply. That possibility was of relevance, especially in patients with high rectal anomalies, where there was a high incidence of associated sacral agenesis.

However, two further autopsy specimens of cases of sacral agenesis (Smith, 1959) had revealed a normal complement of sacral nerves, despite lack of bony development. It was therefore anticipated that continence might be possible in spite of sacral agenesis.

Four patients with high rectal anomalies and associated severe sacral agenesis who had definite evidence of continence after rectoplasty were reported in the present paper. Those findings had indicated the need for additional tests to assess subsequent rectal continence, when an anomalous sacrum had been revealed on radiographic study.

Two tests had been found useful in the pre-operative determination of the integrity of the nerve supply and action of the pubo-rectalis muscle. The tests were described. The detection of perineal skin anæsthesia was good evidence for lack of innervation of the sphincters,

[1] This paper is to be published in full elsewhere.

because the same sacral nerve roots were involved in supplying both the perineal skin and the levator ani. Conversely, the infant's response to pin-prick by upward movement of the perineum was suggestive evidence for sphincter control. However, the most valuable test was the measurement of bladder and urethral function. Those structures were innervated by the same sacral roots as supplied the pubo-rectalis. The clinical assessment of urinary continence, the expressibility of the bladder and the findings of micturition cystourethrography (with, if possible, electromanometric pressure measurements of the bladder and urethra) provided certain evidence of the presence or otherwise of a neurogenic bladder, and therefore measureable evidence of the likely function of the more concealed pubo-rectalis muscle.

The radiological finding of an abnormal sacrum in cases of imperforate rectum put the clinician on guard, but the two tests described were the chief guide in determining the surgical management and in estimating the future function of the sphincters.

DR. F. DOUGLAS STEPHENS (Melbourne) commented that continence of fæces depended on an intact levator ani muscle. Children with "continence" could control flatus and solid motions, but were unable to check liquid motions. Such liquid motions were mainly due to diarrhœa and changes in diet (for example, orange juice). Another problem was being "wet" from mucus discharging from the lower sleeve of mucosa. However, with intelligent care they did extremely well.

Choledochal Cysts.

DR. A. MURRAY CLARKE (Melbourne) read a paper entitled "Choledochal Cysts" (see issue of October 21, 1961.).

DR. H. N. B. WETTENHALL (Melbourne) said he believed that the paper's chief value was in drawing attention to the occurrence of the condition. Differential diagnosis was a problem, and in his ward were two cases in which Wilms' tumour and mesenteric cyst had been considered. Dr. Wettenhall believed laparotomy was probably the best help in diagnosis and asked what value could be placed on a cholecystogram.

Dr. H. Hiller (Melbourne) stated he had no personal experience, but doubted if dye would enter the cyst or be concentrated enough to give a diagnosis.

Social Care of Finnish Children.

PROFESSOR NIILO HALLMAN, Professor of Pædiatrics at the University of Helsinki, Finland, read a paper entitled "Social Care of Children in Finland". Professor Hallman described general conditions in Finland and explained the legislation concerning social care of children in that country. Allowances were distributed to all without regard for means; the most important, perhaps, was the maternity allowance. It was granted on the presentation, before the end of the fourth month of pregnancy, of a certificate issued by a maternity health centre or a private physician. That procedure ensured that every expectant mother reported for a check-up. The benefit was given either as money or as a maternity package, which included all the simple equipment needed in the care of the new-born. A child allowance was paid to the mother for all children under 16 years of age. If the child in question was physically or mentally sick and was nursed at home, the benefit was considerably greater. In addition to the direct benefits, for children and youths who were still studying a deduction was made from the taxable income of the parents. A family allowance was paid only in certain income brackets. Furthermore, it was possible to get loans for the purchase of a home.

The 1944 law on children's welfare centres prescribed that every commune must have at least one district nurse per 4000 or part of 4000 inhabitants. This health worker was in charge of the children's welfare centres, of which there were one or two depending on the size of the district. Every commune was similarly liable to employ a midwife to look after expectant mothers. The majority of the deliveries took place in maternity hospitals. Only about 10% of the babies were born at home, attended by the midwife and the physician. The principal task of a rural midwife was maternity welfare. In rural districts both the midwife and the communal health worker lived in the health centre, which also housed the maternity and children's welfare centres. That ensured the smooth cooperation between the midwife and the communal health worker. The maternity hospital notified the communal health worker of the district by letter of every infant born. In towns and also in rural districts the duties of the health worker included visiting the new-born during the first month of life. Welfare centre work in the rural districts was managed by the local medical officer. In towns those duties were naturally entrusted to specialists.

The children's welfare centre activity was commenced in Finland in the 1920's. Since the founding of those centres was decreed by law the number of children attending them had grown steadily. According to the most recent statistics, the health centre registers listed 68% of infants under the age of one month and 94% of all infants under one year. It was mentioned that visits to the welfare centre were not obligatory. Some children still attended private practitioners for the corresponding advice.

One very important person, whose salary was paid by the local authorities, was the so-called "homemaker". The homemakers gained their training in special schools. Their duty was to replace the mother when she was ill or for other reasons not able to take care of her home. A special training for homemakers was needed because the replacement of a mother required both practical and theoretical skill.

Urban schools had their own physicians and health workers. In rural districts the duties of the communal health worker in charge of the children's welfare centres also encompassed the responsibilities of school health worker. The local medical officer was also the physician in rural districts. The Act on school dentists foresaw school dentists in every commune. However, so far there were several rural communes without a school dentist. It had therefore proved necessary to organize mobile dental centres. Testing of vision and hearing of children in remote districts was done similarly by a system of mobile outpatient clinics. It was worthy of mention that all primary school children had a free meal at school.

The vaccination programme included the inoculations customary in Finland: triple vaccination, vaccination against smallpox and at the present time also poliomyelitis vaccination. In addition, the new-born were vaccinated against tuberculosis at the age of three to five days. That vaccination had been performed since 1947. None of the vaccinations were obligatory. In spite of this it could be said without exaggeration that the vaccination against tuberculosis was at least 100%. The success of the vaccination was controlled by tuberculin testing at the children's welfare centres. The test was repeated when the child was one year old, once at the age of two to three years and several times at school. If the response was negative the test was repeated. A total of over 100,000 vaccinations was performed per year.

PROFESSOR T. STAPLETON (Sydney) expressed his pleasure that Professor Hallman had been able to visit the meeting. Professor Stapleton had been impressed by children's hospitals in Finland. In those hospitals he had noticed the highest standards of scientific and research work combined with a fine psychological approach to the children, which achieved a very happy atmosphere. In many hospitals in other countries that combination was not nearly so well balanced.

DR. ELIZABETH WILMOT (Melbourne) mentioned how impressed she was by provision in Finland of a meal at school for children. Dr. Wilmot asked how expensive that programme was, and who bore the cost.

Professor Hallman replied that each meal cost one shilling, and that some 400,000 children received a meal each day. The expense was met partly by the Government and partly by the local community.

DR. R. SOUTHBY (Melbourne) asked how much of the obstetrics was done by midwives in Finland, who was responsible for the training of homemakers and at what age vaccination against smallpox was performed.

Professor Hallman replied that 95% of babies were born in hospitals, and that midwives were concerned mainly with the preventive aspects of obstetrics. In reply to the second question, he stated that training of homemakers was done in part by private welfare associations, and in part was controlled by the ministry of social affairs. In Helsinki there were several large schools especially for that purpose with an intake of 300 new pupils per year. There was a high loss for marriage, but the training was useful to those students later on. The answer to Dr. Southby's third question was that vaccination was not compulsory and was usually performed after triple antigen inoculation at the age of four months, while vaccination for poliomyelitis was done at the age of six to seven months.

Mental Retardation.

DR. F. GRUNSEIT (Sydney) read a paper entitled "The Diagnosis of Mental Retardation" (see page 615).

DR. A. N. JENNINGS (Sydney), in opening the discussion, agreed that diagnosis of mental retardation was of great importance; as Dr. Grunseit had pointed out, diagnosis extended beyond identifying the condition itself and passed into an assessment of the child in relation to his family. Obviously the problem of a retarded child in a family with few reserves was entirely different from that of an equally retarded child in an accepting family living in an area with good facilities for the education of a retarded child and counselling and support for the family. Chronic handicaps and limitations involved so many factors that it was impossible to generalize about management. That seemed particularly true when the handicap could be recognized at birth, before the mother-child relationship had been established. That was because a most important aspect of the framework for a management programme had not yet developed.

Dr. Jennings, speaking as one who worked in a service where children were placed when the family was unable to care for them, discussed the management of mentally retarded children, taking mongols as an example. Normally, in a child in the middle range of retardation, the handicap would not be recognized until he was about six to nine months old. During that time the infant would have released the maternal drive and would have benefited in his early social and emotional development from maternal care (as Dr. Grunseit had pointed out, mongols did better at home). He referred to the release mechanisms that Bowlby described in the earliest phases of the mother-child relationship. He estimated that about 60 mongols were born each year in New South Wales (the figures came from the Sydney obstetric hospitals) and about three-quarters of them lived at home. The other quarter were placed away from home from birth, some with the "extreme" advice for the mother never to see the baby.

Dr. Jennings stated that one quite frequently saw parents confused by the advice that they had received. Some were paying more than they could afford for their infant mongol in residential nurseries, while some believed the baby was a kind of monster, and dared not take the child home, although that might be an instinctive need. When the parents had received an early recommendation to place the child away from home, the later management programme became very much more difficult. The situation could arise when a child handicapped by mongolism then had a most severe additional handicap—namely, no relative to care for him.

DR. C. P. WALKER (Sydney) expressed a particular interest in the subject. He thought that in some cases of behaviour disorder in childhood before the courts, the judge should call for the obstetrical history. Dr. Walker mentioned that sufferers from Klinefelter's syndrome could go about getting into sexual troubles when the fault lay in their chromosomes. He believed that more psychiatric assessment of such cases was desirable.

Unusual Causes of Steatorrhœa.

DR. CHARLOTTE ANDERSON (Melbourne) read a paper entitled "Unusual Causes of Steatorrhœa in Young Children" (see page 617).

PROFESSOR D. HUBBLE (England) expressed a particular interest in the patient with hypo-β-lipoproteinæmia, that patient being similar in many ways to the patient with complete absence of β-lipoprotein reported by Salt *et alii* (1960). He thought that β-lipoprotein was involved in transport of fat across the small intestinal mucosa, and also in maintaining the integrity of the red blood cell envelope. He believed that the blood levels of β-lipoprotein in Dr. Anderson's patient might have been adequate to prevent acanthocytosis of the red cells. It was hoped that enzymatic studies might elucidate the abnormality. Professor Hubble asked Dr. Anderson if she had encountered steatorrhœa due to temporarily lowered pancreatic enzyme activity following gastro-enteritis, as other workers had reported.

Dr. Anderson replied that she had had no opportunity to investigate patients of that type.

DR. L. TAFT (Melbourne) asked whether any electron-microscopic study of the mucosal cells had been performed. Recent reports had suggested that that technique might be rewarding in the study of absorption.

Dr. Anderson replied that no such studies had been performed, but it was hoped to remedy that in the future.

DR. CLAIR ISBISTER (Sydney) asked Dr. Anderson what criteria she used in making the diagnosis of steatorrhœa.

Dr. Anderson replied that the diagnosis was a biochemical one. Fat intake in the diet and fat output in the fæces were estimated over a period of three to eight days. An average output of more than 4 grammes per day constituted steatorrhœa.

The Electrocardiogram QT and Rheumatic Carditis.

DR. D. C. FISON (Brisbane) read a paper entitled "The Electrocardiogram *QT* and Rheumatic Carditis" (see page 622).

PROFESSOR W. MACFARLANE (Australian National University) pointed out that in isolated muscle fibres the *QT* interval was decreased immediately after injury. He wondered whether the finding of an increased *QT* interval reflected some recovery of the myocardium, and asked Dr. Fison how early his cases of rheumatic fever were.

Dr. Fison replied that electrocardiograms were taken between three and seven days after the onset of symptoms.

DR. H. HILLER (Melbourne) stated that in his experience a number of febrile and toxic states (for example, osteomyelitis and staphylococcal pneumonia) were accompanied by a grossly increased *QT* interval, in many cases greater than that seen in rheumatic fever. That lack of specificity was the reason why he had abandoned the test as a diagnostic measure.

Dr. Fison in reply agreed that many diseased states could be accompanied by a prolonged *QT* interval, but that the measurement seemed to him to be as useful as determination of the *PR* interval.

Chemotherapy in Acute Leukæmia.

DR. J. H. COLEBATCH (Melbourne) read a paper entitled "Chemotherapy and Remission in Acute Leukæmia in Children" (see page 624).

DR. I. S. WALLMAN (Perth) asked Dr. Colebatch whether administration of 6-mercaptopurine for an extended period was more beneficial than cessation of the drug as soon as remission was achieved, with resumption of 6-mercaptopurine therapy when exacerbation of the disease occurred.

Dr. Colebatch replied that his opinion, and the opinion of every clinic dealing with leukæmia, was that it was advantageous to continue 6-mercaptopurine therapy after remission had been achieved.

DR. S. W. WILLIAMS (Melbourne) commented that in his experience complications of antibiotic therapy (such as proctitis, moniliasis and so on) occurred only in patients with leukæmia. He asked Dr. Colebatch's opinion on that facet of the disease.

Dr. Colebatch pointed out that leukæmia itself lowered resistance to infection, that 6-mercaptopurine suppressed antibody production and that steroids were known to increase susceptibility to infection. The decision on when to give antibiotics to patients with leukæmia was often difficult, and required considerable judgement.

PROFESSOR DE SILVA (Ceylon) asked Dr. Colebatch whether the increased incidence of leukæmia was real, or only apparent.

Dr. Colebatch replied that most workers thought that the increase was a real one.

Erythrocyte Enzyme Deficiency and Hæmolytic Anæmia.

DR. L. I. TAFT (Melbourne) read a paper entitled "Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency".

Dr. Taft stated that in the previous decade 12 patients originally presenting with attacks of acute acquired hæmolytic anæmia at the Royal Children's Hospital, Melbourne, had since been shown to be deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) in their red cells.

The patients' ages ranged from five months to 12 years, most attacks occurring under the age of four years. There were nine males and three females, all of Mediterranean origin and mostly of Greek extraction. They had suffered a total of 17 attacks, three patients having had multiple episodes. Ingestion of the common broad bean (*Vicia faba*) had preceded at least nine of the hæmolytic attacks, and probably a further two; naphthalene moth-ball ingestion had precipitated one attack. In no case was there a family history of hæmolytic anæmia, or a past history of hæmolytic disease of the new-born or congenital non-spherocytic hæmolytic anæmia.

Within 24 to 48 hours of the ingestion of the precipitating factor the patients had become feverish, with severe pallor, vomiting and red urine. Subsequently there had been jaundice, while the spleen occasionally had been able to be felt and the urine had been dark in colour.

On admission there had been anæmia, frequently severe, with leucocytosis and reticulocytosis. The indirect-reacting serum bilirubin level had been elevated, also the urinary urobilinogen content, and hæmoglobin had been identified in the urine. The Coombs test had given a negative result in all cases but one.

Single transfusions had been given on 12 occasions; cortisone administration in one case had had no apparent effect on the clinical course. Hæmolysis had ceased within three to four days, and with observation of the fluid balance, no renal complications of the hæmoglobinuria had been encountered. There had been no evidence of chronic anæmia between the attacks and all patients had since been well.

The enzyme G6PD was of importance in the maintenance of reduced glutathione levels in the red cells. With G6PD deficiency those levels tended to be low, and if the red cells were incubated with certain drugs (for example, acetylphenylhydrazine as in the glutathione stability test), the level of reduced glutathione was greatly reduced, whilst in normals it was hardly affected. Glutathione stability tests and direct enzyme assays had been performed at least some weeks after the anæmia and reticulocytosis had disappeared.

The results of the blood glutathione stability tests and enzyme assays in normals and in the susceptible "reactors" were generally in agreement with published values, and while some borderline cases were encountered in each of the tests, the combination of all three, particularly the enzyme assay, accurately confirmed the diagnosis of G6PD deficiency.

In one family the maternal grandfather of the male patient was also shown to be deficient in G6PD, although his mother had normal levels of enzyme; this confirmed the sex-linked mode of transmission, and accounted for the male preponderance in the series. However, the occurrence of some female reactors suggested a variable penetrance of the defect, and of seven mothers of patients four showed enzyme levels lower than normal. These female "intermediates" could not be detected by the glutathione stability tests.

The glutathione stability test was usually diagnostic, but in suggestive cases with a normal or borderline result, and in family studies especially with female patients, direct enzyme assays were desirable. Reactors should be warned of the hazards of poorly-cooked broad beans, naphthalene moth balls and drugs such as sulphonamides and nitrofuradantin, which were likely to precipitate hæmolytic episodes. Favism was now not an uncommon disease in Australia and the enzyme deficiency predisposing to it could be readily confirmed in the laboratory. Its recognition was of importance in prophylaxis and in avoiding unnecessary treatment (for example, steroids or splenectomy).

This paper is to be published in full elsewhere.

Acute Hæmolytic Anæmia.

DR. J. D. HARLEY (Sydney) read a paper entitled "Acute Hæmolytic Anæmia in Australian Children of Mediterranean Racial Extraction".

Dr. Harley reviewed certain clinical and biochemical features of 12 Mediterranean children admitted to the Royal Alexandra Hospital for Children with acute hæmolytic anæmia, with three additional cases already reported in the Australian medical literature. Three of these children had each sustained two, and one child three acute hæmolytic episodes, so that a total of 20 episodes had occurred in the 15 children under review.

Of the 15 children, 13 were male, and of the 20 hæmolytic episodes, 13 had occurred in the Australian springtime. The age of onset was less than four weeks in three, less than one year in six, and less than four years in 16 of the 20 episodes, but ranged to 10 years in the remaining four children. Most emphasis was thus on the earlier years of childhood. The racial background was Italian in seven children (with only one from Sicily and no known derivation from the island of Sardinia) and Greek in eight; five were from the eastern chain of Greek islands and one was of mixed Greek, Syrian and Egyptian extraction.

Ingestion of the Australian broad bean, *Vicia faba,* had closely preceded the onset of nine hæmolytic episodes. One new-born infant had developed severe hyperbilirubinæmia, with evidence of excessive hæmolysis after the injection of 2 mg. of a vitamin K analogue, and another after possible exposure to phenacetin and acetylsalicylic acid in the breast milk of the mother. One older infant had developed acute hæmolytic anæmia with an illness indistinguishable from acute glomerulonephritis, and one child had sustained a mild hæmolytic episode in association with intestinal salmonellosis. Of the seven remaining episodes in which the ætiological agent was unknown, five had occurred in ambulant males in springtime, one in an infant receiving maternal breast milk, and one in a new-born infant with marked hyperbilirubinæmia.

The erythrocyte glucose-6-phosphate dehydrogenase (G6PD) activity in the 13 children tested (0 to 93 units per 100 ml. of erythrocytes) had been well below the range obtained in a group of either normal Anglo-Saxon children (134 to 201 units per 100 ml. of erythrocytes) or of normal Mediterranean children (128 to 204 units per 100 ml. of erythrocytes). In 10 of the affected children, the G6PD activity had been less than 30 units per 100 ml. of erythrocytes. When erythrocytes from those 10 children were incubated with acetyl phenylhydrazine, marked degrees of instability of reduced glutathione (GSH) and susceptibility to Heinz body formation had also been found. Such marked erythrocyte defects were characteristically found in ambulant males whose illness occurred in the springtime, with or without known ingestion of *Vicia faba.*

The association of severe neonatal hyperbilirubinæmia with erythrocyte G6PD deficiency had been found in three infants, of whom one had subsequently sustained an attack of favism. The relatively higher G6PD levels of 64 and 93 units per 100 ml. of erythrocytes in two of these new-born infants had been taken to reflect the higher G6PD activity of the normal neonatal period.

In discussing these findings, Dr. Harley suggested that the high male incidence might be related to the mode of genetic transmission of G6PD deficiency, and the seasonal incidence to the germination and flowering of *Vicia faba;* but he pointed out that no explanation was apparent for the relative infrequency of that syndrome in older children or adults, or for the paucity in ambulant children of noxious agents other than *Vicia faba.* The importance was also stressed of an awareness of the syndrome of neonatal jaundice associated with G6PD deficiency, and of protecting new-born infants from potentially hæmolytic agents.

Dr. Harley then discussed the relationship of G6PD deficiency, GSH instability and susceptibility to Heinz body formation to drug-induced hæmolysis *in vivo.* Certain drugs damaged the erythrocyte by destroying hæmoglobin and producing Heinz bodies, or by an independent effect which led to increased osmotic fragility, or by both mechanisms. Reduced glutathione (GSH) appeared to play an essential part in protecting both the hæmoglobin and the cell membrane from drug-induced destruction. Glutathione was maintained in its reduced form by the oxidation of glucose-6-phosphate via the pentose phosphate pathway, which utilized the enzyme G6PD. The inability of the G6PD-deficient cell to protect GSH when challenged with certain drugs might thus lead to increased susceptibility to hæmoglobin destruction, Heinz body production, reduced osmotic fragility and loss of cell integrity.

In conclusion, the observations were taken to emphasize the varied manifestations of G6PD deficiency in childhood. New-born infants were prone to severe hyperbilirubinæmia and kernicterus, both with and without known exposure to hæmolytic agents. Such agents might reach the infant from either the maternal circulation or the maternal breast milk. Older children were susceptible to the hæmolytic effect of *Vicia faba* and a wide range of chemical substances. Adults also might be susceptible, and the absence of Australian reports of drug-induced hæmolysis in G6PD-deficient adults was unexplained. The racial incidence of the defect directed particular attention in Australia to the members of Mediterranean racial groups. Furthermore, the defect was congenital and genetically determined, so that subjects with a personal or family history of neonatal jaundice, drug-induced hæmolysis or favism must be regarded as potentially susceptible. Those considerations served to emphasize the importance of lifelong protection of such potentially susceptible individuals from the wide range of potentially hæmolytic agents.

This paper is to be published in full elsewhere.

PROFESSOR L. DODS (Sydney), opening the discussion, quoted the public health wisdom of Pythagoras: "Keep your hand from beans which is a harmful food". He mentioned that, although the ratio of Italians to Greeks in Australia was 3:1, there was a higher incidence of Greeks among

reported cases of G6PD deficiency. There was a need for awareness of the danger to some children of that stock. Professor Dods urged a different approach for dealing with new-born babies of Mediterranean extraction. Administration of drugs such as vitamin K, sulphonamides, chloramphenicol or A.P.C. to those babies, or to their mothers in the prenatal period, could be hazardous. Professor Dods inquired if it was possible to establish the potential ability of a substance to produce hæmolysis in reactors by in-vitro testing.

Dr. Taft replied that some drugs could be shown *in vitro* to be potentially harmful, but he was unaware of any wide-scale investigation having been performed. One of the patients in his series had developed a hæmolytic episode after contact with a well-known medicament which was rubbed on the chest, and had presented just that problem.

Dr. Harley added that the glutathione stability test was probably the best in-vitro means of predicting the effect of test substances on sensitive erythrocytes. In recent years marked glutathione instability had been shown in G6PD deficient cells after incubation with the beans, pollen and pistils of *Vicia faba*. The failure of some substances which produced hæmolysis *in vivo* to cause in-vitro changes might be related to the production of active degradation products *in vivo*. For example, naphthalene was inactive *in vitro*, but the metabolic degradation products, β-naphthol and α- and β-naphthoquinone were active.

DR. J. COLEBATCH (Melbourne) asked (i) whether there was a safe dose of vitamin K analogue which could be given to susceptible babies, or whether the drug should not be used; and (ii) whether there was any evidence that vitamin E deficiency played a part in the susceptibility to hæmolysis, as suggested by the experimental work of Gordon.

In reply to Dr. Colebatch, Dr. Harley said that the available evidence suggested that a dose of 2 mg. of certain vitamin K analogues was quite sufficient to produce excessive hæmolysis with hyperbilirubinæmia in a new-born infant with G6PD deficient erythrocytes. He suggested that the dose of 1 mg. should not be exceeded in new-born infants of Mediterranean extraction, and that vitamin K analogues should be avoided if possible in any such infant with a personal or family history of neonatal jaundice, favism or drug-induced hæmolysis. Although vitamin E had been shown to protect rats from the hæmolytic effect of vitamin K, there was no evidence to suggest that vitamin E deficiency was a significant factor in drug-induced hæmolysis in human subjects.

Professor Hubble pointed out the advantages in mixing ethnic groups in the population. That allowed study of diseases which would not otherwise be encountered in the locality (for example, sickle-cell anæmia and congenital syphilis had been found in some migrant Jamaicans in Birmingham), and also allowed study of the effects of displacement of children.

Professor de Silva commented on the relatively common occurrence of neonatal jaundice in the Chinese population of Singapore. He believed that some cases of hyperbilirubinæmia had the basis referred to in the papers of Dr. Taft and Dr. Harley. Professor de Silva remarked on an increase in the incidence of hyperbilirubinæmia and kernicterus which had occurred since hypotensive agents and chlorpromazine had been more commonly used.

Follow-Up of Achlorhydria in Children.

DR. R. SOUTHBY (Melbourne) read a paper entitled "Achlorhydria in Children—Some Follow-up Experiences" (see page 628).

DR. C. E. RICHARDSON (Ballarat) commented that he had had considerable success using treatment with hydrochloric acid in the diarrhœal and anæmic types of case, but could not enthuse about the results he had achieved in the allergic type of case.

DR. D. G. HAMILTON (Sydney) expressed his firm conviction that acid helped in many cases. It was his policy to give hydrochloric acid if a child did not fall into any easily diagnosable category. Fifty *per centum* of those children benefited, and the remainder did not, but no reason had been apparent. Dr. Hamilton believed that allergic children obtained benefit from acid only when there were symptoms of digestive upset.

DR. KATE CAMPBELL (Melbourne) commented on the value of long-term surveys such as that of Dr. Southby, and asked whether a proprietary preparation in which hydrochloric acid was enclosed in a gelatin capsule was useful.

Dr. Southby replied that he had had little experience with the new preparation as yet, but believed that it might be useful in older children. It was difficult to get infants to take capsules.

Chromosomal Disorders in Childhood.

PROFESSOR DOUGLAS HUBBLE (England) read a paper entitled "Chromosomal Disorders in Childhood".

Professor Hubble began by relating the discovery of nuclear sexing by Barry and his colleagues and describing the methods which were used in the buccal mucosal smear and in leucocytes for determining sex. Then he described the advance in the study of human chromosomes, beginning with the discovery by Tjio and Levan that there were 46 and not 48 human chromosomes. Barry identified the sex chromatin in the nuclei with the pair of sex chromosomes in the female. There were, however, difficulties in that interpretation, since half the female nuclei showed no sex chromatin and none were seen in the male nuclei (XY). One hypothesis which fitted most of the known facts was that one set of autosomes was sufficient to suppress the chromatin in one X but not in XX. Thus patients with XXX showed two chromatin bodies in the nuclei.

He then mentioned the various mechanisms which caused chromosomal disorders, such as non-conjugation, translocation and deletion. Non-conjugation during gametogenesis produced the well-known conditions of sex chromosomal abnormalities such as Turner's syndrome and Klinefelter's syndrome. Non-conjugation during mitosis, however, produced mosaicism of the sex chromosomes, of which examples were being more frequently recorded. The abnormalities of the autosomes which had been described had been due both to non-conjugation and to translocation. Translocation of a small fragment could be detected in meiosis only, but when a large fragment was attached to a non-homologous chromosome, that could be detected in mitosis.

Professor Hubble then described the methods of chromosomal counting in human cytology—in skin, bone marrow and blood—and said that the leucocytes provided the easiest method in routine laboratories, but mosaicism was not always revealed in that way. He referred to the Denver Convention (1960) method of enumeration which was now accepted everywhere.

He then proceeded to discuss the differential diagnoses of patients with intersex, describing a case of male pseudohermaphroditism in which a girl, aged three years, presented with normal external genitalia, but an enlarged phallus. No gonads were identifiable. The buccal mucosal smear showed chromatin-negative nuclei, but a vaginogram showed a normal vagina, a tiny urethra and Fallopian tubes. A chromosomal count confirmed the buccal mucosal smear investigation and showed 46 chromosomes (XY). A laparotomy revealed one gonad only, which was placed below the right kidney and was male.

Two cases of Turner's syndrome were then described, both of which had persisted into the third year of life. In the case of the first patient, aged only two years, the gonadotropin output was more than 30 mμ per 24 hours. Professor Hubble then described a patient, aged 16 years, with the characteristic somatic abnormalities of Turner's syndrome; in this case a mistake in nuclear sexing had been made when the patient was aged 10 years, and to the surprise of the pædiatrician concerned, the girl had proceeded to a normal puberty and had had regular menses since. Later examination of the buccal mucosal smear and the chromosomes showed that the patient had XX chromosomal complement. He referred to the fact that the reason why ovarian agenesis was associated with stereotyped somatic abnormalities was quite unknown, though some geneticists attributed that to lack of genetic process between chromosomes. However, such a case as the one described established clearly that the somatic abnormalities characteristic of Turner's syndrome might exist without ovarian agenesis. A case of Turner's syndrome was then described and Professor Hubble suggested that the XX constitution might not only be associated with long legs and hyaline degeneration of the testes, but also with a homosexual disposition.

A case in which there was triple mosaicism was then discussed. A girl, aged 10 years, with short stature and with some of the features of Turner's syndrome, had a buccal mucosal smear showing a reduced number of chromatin-positive cells ranging from 1% to 26%. Twelve *per centum* of those nuclei had double Barr chromatin bodies. She was shown, by a chromosomal examination to have an XO/XX/XXX chromosomal complement. Professor Hubble referred to the fact that one other patient had been proven

to be suffering from triple mosaicism by Hayward working in his department. That patient had suffered from long-segment Hirschsprung's disease, but other patients of the same sort had been investigated without the discovery of triple mosaicism having been made.

He then turned to autosomal abnormalities, enumerating the disorders with which trisomy had so far been discovered to be associated; he included in his remarks chromosome 21 (mongolism) and chromosomes 15, 17, 19 and 22. He gave a detailed account of two patients with abnormal autosomal trisomy which had been discovered in his department; the first patient had multiple abnormalities associated with trisomy for 17, a variety reported by J. H. Edwards and his colleagues, and another patient had the Sturge-Weber syndrome with a trisomy for 22 and had already been reported by Hayward and Barr. However, Hayward and Barr had investigated eight other cases of Sturge-Weber syndrome without finding that abnormality, and other workers had reported negative findings in seven other cases. That emphasized the fact that the finding of chromosomal abnormality in conjunction with any known syndrome did not necessarily mean that there was a causal association between those two findings; the chromosomal abnormality might simply be an expression of some underlying cause which, in the case of the chromosomes, had been expressed at the nuclear level. Professor Hubble referred briefly to the finding of an abnormal chromosome in chronic myelogenous leukæmia (21 or 22), and discussed its possible relationship to the acute leukæmia occurring in mongolism (21). He emphasized that there was a wide field for further chromosomal investigations, and no study of the subject in relation to fœtal loss had yet been undertaken. It would be many years before scientists began to identify the genes on the chromosomes, of which there were probably more than 60,000. One might soon hope that a select number of clinical abnormalities (such as mongolism, whose relationship to trisomy should be accepted as already proven) would be able to be related to chromosomal abnormalities.

DR. DOUGLAS GALBRAITH (Melbourne) mentioned the frequent occurrence of microdactyly in myositis ossificans progressiva as an example of an association of a somatic defect with a biochemical aberration, and asked Professor Hubble if any chromosomal abnormality had been found responsible.

Professor Hubble replied that no such abnormality had been found in the disease mentioned by Dr. Galbraith, or in a number of other diseases similarly investigated. Professor Hubble pointed out that there might be no morphological evidence of a single genetic defect on examination of chromosomes.

DR. M. J. ROBINSON (Melbourne) mentioned a patient conforming to the features of the Bonnevie-Ulrich syndrome. He asked Professor Hubble if it was right to expect the chromosomal count to be normal—that is, not XO.

Professor Hubble answered that a normal count would be expected, but that a chromosomal count should nonetheless be done.

DR. J. H. COLEBATCH (Melbourne) asked how far one was justified in saying that a chromosomal abnormality, when found, was hereditary. He asked whether many chromosomal aberrations could be the result of factors operating in early intrauterine life.

Professor Hubble said that mitotic abnormalities were not heritable, but that even meiotic ones might not go back far in the family tree. Most of the patients whom he had discussed did not have inherited defects. The familial occurrence of Turner's syndrome and Klinefelter's syndrome was most unusual.

Addison's Disease in Three Siblings.

DR. HOWARD WILLIAMS (Melbourne) read a paper on "Primary Familial Addison's Disease". Dr. Williams reported a remarkable family in which three children had proven adrenal hypofunction.

He said that adrenal insufficiency was uncommon in children, and that when it occurred in more than one member of a family, it was usually one aspect of a syndrome and not a primary disorder of the adrenal glands. For example, adrenal cortical insufficiency, hypoparathyroidism and chronic moniliasis were one such syndrome; adrenal cortical insufficiency in association with either congenital adrenal hyperplasia, familial spastic paraplegia, diabetes mellitus or certain thyroid disorders were other syndromes.

The family he was reporting was remarkable in that three children out of five had clinical and biochemical features of partial adrenal cortical failure. One other child had died at the age of seven years after recurrent fits, and the cause of death was unknown. The remaining child and the parents, who were second cousins, were alive and healthy and had normal adrenal function.

The three affected children, whose ages were thirteen, eight and five years respectively, had certain common features. Growth and development had been normal until the children had reached the ages of nine, five and four years respectively, and none of them had had any serious illness. Then gradually they became languid and tired easily, and developed abnormal pigmentation which was most pronounced in the gums, the exposed parts of the body (such as the back of the fingers and hands and the front of the knees) and also in the nipples and umbilicus. The elder boy developed pigmentation in two operation scars. Two of the children developed aches and pains in the limbs and numbness and tingling in the fingers. Two developed some puffiness of the face. None of them had a craving for salt.

When examined none looked in any way ill and the only abnormal physical finding was pigmentation of the gums, the exposed parts of the body, the nipples and the umbilical area. Investigation of adrenal function by stimulation with corticotrophin showed a negligible response. The level of 17-hydroxycorticosteroids in the urine was low and remained low during stimulation with ACTH, which was given intramuscularly as a gel. In the elder boy a blood corticosteroid level test resulted in a zero reading during ACTH stimulation. The 17-ketosteroid level also showed an insignificant rise during such stimulation and the eosinophil count did not change. All the tests were repeated on several occasions during a two-year period, and the results in Dr. Williams's own laboratory and in two other laboratories were the same.

By contrast there was no significant disturbance of water and electrolyte metabolism. Serum electrolyte levels were normal each time the tests were repeated, the sweat test gave a normal result and two of the three patients, when placed on a low-sodium diet, conserved sodium well. A urine assay of one patient for aldosterone showed that it was present, but the amount was not quantitatively measured.

Dr. Williams concluded that the adrenal biochemical defect at the time of investigation showed involvement of corticoid activity of the gland, while aldosterone activity did not seem to be similarly depressed.

The pathological nature of the adrenal lesion could only be inferred. An acquired destructive lesion of the adrenals from tuberculosis or other causes was excluded on the grounds that there was no evidence for such a lesion and the chances of such a lesion affecting three members of a family were practically nil.

An auto-immune phenomenon was excluded on the evidence that there were no circulating antibodies against human adrenal antigen.

Cortical atrophy seemed to be the most likely cause, as it had been observed in three other families in which there were two affected siblings. However, an enzyme deficiency involving the synthesis of corticosterone could not be excluded on the available evidence.

This paper is to be published in full elsewhere.

DR. M. J. ROBINSON (Melbourne) commented that he had been concerned with a child believed to have adrenal hypoplasia, and that Dr. Alan Williams had searched the autopsy reports at the Royal Children's Hospital, and had found records of two patients who had died from adrenal hypofunction. There was experimental evidence in animals that adrenal cortical regeneration could occur. Dr. Robinson mentioned a child with temporary adrenal insufficiency, who had needed cortisone and salt for two months and then had recovered.

DR. H. N. B. WETTENHALL (Melbourne) stated that there was much about Addison's disease in children that was unknown. He also had a patient needing cortisone who, he believed, would recover spontaneously.

DR. D. B. CHEEK (Melbourne) said that the failure of ACTH to stimulate cortisol production was of interest. That such children had no detectable disturbance of electrolyte balance—yet insufficiency of hydrocortisone—indicated once again that aldosterone was governed by a separate hormone that stimulated the strata glomerulosa. Dr. Cheek mentioned a recently developed micro-assay technique using *d-l* aldo-

sterone and the whole body electrolyte of mice.[1] Doses as small as 0·0001 μg. of *d-l* aldosterone caused a significant alteration in body composition. When 1/200 of the 24-hour urine sample of the youngest (but untreated) child of the family was injected into 50 day old mice, a loss of sodium, potassium and water was demonstrated over and above that found in the control mice. This suggested the presence of adequate amounts of aldosterone in the urine of the child.

(To be continued.)

Out of the Past.

SOME SOUTH AUSTRALIAN MEDICAL VETERANS.[1]

[From the *Australasian Medical Gazette*, February 20, 1903.]

IT is somewhat surprising to find such a comparatively large number of veteran practitioners in the ranks of the profession in South Australia, the names of several having been on the medical register for more than 40 years. Dr. James Phillips can claim the distinction of being the "grand old man" of the medical profession in South Australia. He was admitted as a member of the Royal College of Surgeons in England in 1843, and was enrolled as a practitioner in this State on April 3, 1849. Dr. Robert Tracey Wilde was also admitted to the Royal College of Surgeons in 1843, but was not registered in Adelaide until July, 1850. Dr. Morgan Thomas began practice in South Australia on July 5, 1852, having secured his diploma in England in 1847. Dr. Alexander T. Gunning, who is still in active service at Narracoorte, has been enrolled on the local register since July 3, 1855. Those who signed the roll during the sixties were Dr. J. W. D. Bain of Port Germein, whose membership of the Royal College of Surgeons dates from 1864, and who was registered here on August 24, 1865; and Dr. Thomas W. Corbin, who was admitted to the Royal College of Surgeons in the same year as Dr. Bain, and whose local certificate is dated July 31, 1865. Several of those who came to Australia in the next decade are still practising in Adelaide or in the various country districts, but most of them might almost claim to be regarded as young men in comparison with the veterans named above.

Correspondence.

AIR TRANSPORT OF SOME CASUALTIES.

SIR: In a letter published in THE MEDICAL JOURNAL OF AUSTRALIA of July 29, 1961, Dr. P. J. Daly refers to certain risks in air evacuation of cases of penetrating eye wounds and head injuries with cerebral hæmorrhage. He states that, in these cases, "it is really essential to instruct the pilot [of non-pressurized planes] to fly at no more than 2500 ft. altitude . . . ", but that "pressurized civil aircraft . . . are safe at any altitude . . . ".

It is important, first, to be clear on the performance of pressure cabins, since this is often misunderstood. Pressurized aircraft do not maintain ground-level pressure in their cabins at all altitudes, but can maintain a differential pressure between the cabin and external atmosphere up to a certain maximum value characteristic of each aircraft type. This maximum differential usually lies between 5 and 8 p.s.i. Thus, while a pressurized aircraft is flying fairly low, say at 5000 ft., it can maintain ground-level pressure in its cabin. But a Friendship at 15,500 ft., a Viscount at 20,000 ft. and an Electra at 24,500 ft. (quite usual operating altitudes) each has a cabin pressure about the same as that of an unpressurized plane at 5000 ft.

The risks which Daly suggests attend air evacuation of perforating eye injuries are "gaping of the eye wound with possible loss of contents and intraocular hæmorrhage". This notion has been put forward also by Pedriel,[1] but without any supporting evidence as to how a pressure change (if any) in the semi-liquid contents of the eye will result in a volume change. Pinson[2] has shown that there is no change in intraocular tension relative to ambient pressure with altitude even up to 40,000 ft. Volume changes on alteration of atmospheric pressure occur when *gas* is trapped in or cannot reenter a body cavity, as in aerotitis, pneumothorax, intestinal obstruction or in the aerosinusitis which Daly mentions.

Studies of large numbers of air evacuations of military casualties or statements of policy based on such experience (for example, Strickland and Rafferty,[3] Corbet and Nelson[4] and Braswell[5]) reveal no reference to perforating eye wounds as a contraindication to air transport, which is surprising if the hypothetical risks had been actually observed. On the contrary, Meneces[6] and Behrens[7] recommended perforating wounds of the globe for priority air transport.

With regard to head injuries, a volume change due to altitude can only occur if there is an aerocele, as O'Leary[8] has pointed out. Examination of records of the major domestic airlines in this country shows that in a twelve-months period some 46 cases of head injury with intracranial hæmorrhage have been carried by air, all without ill effect.

In any case, the effects of air transport on a patient's condition ought to be compared, not with his condition under immobility, but with the effects of alternative means of transport, which in these cases would be long ambulance rides over indifferent roads. It would be regrettable indeed if patients who could benefit from air transport were to be denied it because of speculative fears.

Yours, etc.

J. C. LANE.

499 Little Collins Street,
Melbourne, C.1.
September 29, 1961.

HYPERTENSION AND LIFE ASSURANCE.

SIR: On arrival back from overseas I find I owe Dr. Woolnough the courtesy of a reply to his letter in THE MEDICAL JOURNAL OF AUSTRALIA of April 29, 1961.

I must succumb to his soft impeachment that I am suggesting that "we" doctors "fudge and fabricate blood pressure readings"—with, however, the qualifications contained in my previous letters of February 25 and April 1, 1961.

With regard to his system of recording blood pressure, I wish to assure Dr. Woolnough that, in my view, his method is in the best tradition—with the proviso, however, that labile hypertension is not lightly regarded. Should he wish, I would be happy to supply him with the essential literature bearing on this aspect from the life assurance angle.

Yours, etc.

W. J. MCCRISTAL.

The City Mutual Life Assurance Society Limited,
Hunter and Bligh Streets,
Sydney.
September 29, 1961.

CORONARY HEART DISEASE.

SIR: I have been an actor in a drama, from which I would gladly have been absent.

"Come quickly, doctor, L—— is dying!"

On the floor of the kitchen the fourteen-year-old son was doing mouth-to-mouth respiration on his dead father. My patient, who had become my friend, was dead at fifty. I'd had coffee with him that morning. Little did I think that already the angel of death was hovering in the wings.

How can you tell when a man is going to die? I suppose the general practitioner sees more people die than any other

[1] *Clin. Sci.*, 1960, 2: 233.

[1] From the original in the Mitchell Library, Sydney.

[1] *Med. Aero.*, 1956, 2: 215.

[2] *J. aviat. Med.*, 1940, 11: 108.

[3] *J. Amer. med. Ass.*, 1951, 145: 129.

[4] *Canad. med. Ass. J.*, 1955, 72: 111.

[5] *Wld. med. J.*, 1956, 3: 111.

[6] *J. roy. Army med. Cps.*, 1951, 96: 1.

[7] Unpublished paper cited in "Abstracts on Military and Aviation Ophthalmology and Visual Sciences", Volume I, 1953; Washington: Biological Sciences Foundation, 1953.

[8] MED. J. AUST., 1961, 11: 373.

branch of the medical profession. In the main he is an experienced and competent observer, and might give the National Heart Foundation some valuable data.

The captains of industry, startled by the mortality among their top men in their prime, and believing that money solves everything, have supplied the sinews of war. Soon they will be asking—what now? We, too, would like to know what are the plans of the N.H.F. I know we cannot expect immediate results.

Any worth-while advance in medicine has come from dedicated first-class brains, usually with no financial encouragement whatsoever. If someone would dip his pen in coronary blood and inspire some of the real researchers, it might be more effective than all the money recently collected. But perhaps I am unduly disheartened.

Yours despondently,

September 17, 1961. H.W.A.

CENTRAL DISTRICT AMBULANCE HEADQUARTERS APPEAL.

SIR: On the fifteenth instant, His Excellency the Governor of New South Wales, Lieutenant-General Sir Eric Woodward, officially opened the new headquarters station of the Central District Ambulance Service. It is hoped that some members of the medical profession will find time to inspect the new building, and see the modern installation for monitoring and recording calls for ambulance attention, as well as the layout and equipment of an up-to-date service.

If was pointed out at the opening ceremony that although we consider that our organization provides the best service possible with the means at our disposal, we are not unaware that improvements could be made in certain directions. We are still unable to meet what should be a minimum requirement—namely, the manning of every ambulance with two trained officers. Working three eight-hour shifts daily, we have only 110 officers to 35 ambulances, distributed over a network of 13 stations. To put the case more succinctly, if we had the money we could provide better service. Our slogan should be: "Give us the means, we'll provide the service."

It may be remembered that last year an appeal, Operation Headquarters, was launched to raise £85,000 towards the cost of our new building. To date donations have totalled some £20,000. To those who generously contributed we are most grateful. The appeal is still hopefully open. Donations may be sent to our new address, 93-105 Quay Street, Sydney. As nobody draws any commission from such donations, every penny will applied to the building fund.

Yours, etc.

93-105 Quay Street, Sydney. A. W. J. BULTEAU.

September 28, 1961.

AUTONOMIC DYSPRAXIA AND DANDRUFF.

SIR: I should appreciate a little space in your columns to reply briefly to a letter by Dr. B. Haynes, which was published in an earlier issue of your Journal.[1] I wish to thank Dr. Haynes for bringing his work to my notice. I am making a study of his Journal articles and expect to receive a copy of the text to which he refers (Haynes[2]) in the near future.

With regard to the two points made by Dr. Haynes, I must give full credit for any claim of a "discovery" to the newspaper concerned, and I should like to correct the newspaper version of a statement in my paper about intermediate mechanisms influencing scurf. Referring to the literature, I said:

> Although general claims have been made that all skin disorders are affected by emotional changes, lists of psychosomatic affections of the skin do not usually include so much as a reference to the dandruff group of conditions. This is not surprising in view of: (*a*) the strong evidence that dandruff is primarily caused by the action of micro-organisms; (*b*) that no direct neurological or physiological mechanism has been demonstrated to link the stratum corneum with those structures in the corium which might be involved in a state of affective arousal.

Yours, etc.

Newcastle University College, Tighe's Hill, 2N., Newcastle, N.S.W. B. FENELON.

September 29, 1961.

[1] MED. J. AUST., 1961, 2: 45 (September 9).

[2] "Autonomic Dyspraxia", 1958, Lewis, London and New York.

THE VIRUS IN THE ÆTIOLOGY OF CANCER.

SIR: Dr. Helene Toolan of New York has since 1953 been growing human tumours in animals (hamsters). All that is necessary is to inject cortisone at the same time she injects the suspension of human cancer cells; she has done it thousands of times. Recently Dr. Toolan has grown from these a virus which causes osteolytic changes when injected into young hamsters. This could possibly be a major breakthrough in our knowledge of human cancer; perhaps this will prove to be cortisone's greatest benefit to mankind.

Since 1909 Peyton Rous has been pointing out that none of the known facts about cancer disproves the virus theory. All that is necessary is for oncologists to become virus-minded and to make use of the enormous advances in virology of the past few years.

Yours, etc.

St. Moritz on-the-Park, 50 Central Park South, New York 19, N.Y., U.S.A. MICHAEL KELLY.

September 26, 1961.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Post-Graduate Conference at Parramatta.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that, in conjunction with the Central Western Medical Association, a post-graduate conference will be held in the Nurses' Lecture Room, Parramatta District Hospital, on Saturday and Sunday, October 21 and 22, 1961. The programme is as follows:

Saturday, October 21: 2 p.m., "Cardiac Emergencies", Dr. J. G. Richards; 2.45 p.m., "Kidney Disease in General Practice", Dr. Ralph Reader; 4 p.m., medical question time.

Sunday, October 22: 10 a.m., "The Value of the Papanicolau Smear", Dr. Mary Heseltine; 11 a.m., "Drugs in Gynæcology", Dr. J. W. Knox; 11.45 a.m., gynæcological question time.

The fee for attendance is £3 3s., and those wishing to attend are requested to notify Dr. C. A. McDermott, 8 Carlton Street, Granville, as soon as possible. Telephone: YU 1570.

Symposium on Skin Cancer.

A symposium on skin cancer has been arranged by the Post-Graduate Committee in Medicine in the University of Sydney in conjunction with the New South Wales State Cancer Council, to be held at the John Belisario Institute of Dermatology, Royal Prince Alfred Hospital, on the afternoon and evening of Wednesday, October 25, 1961. Two overseas doctors will speak at the symposium—Dr. Y. Noguchi of Japan and Dr. G. Weber of Germany. The afternoon session of the symposium will begin at 2 p.m. and conclude at 5.45 p.m. The evening session will begin at 7.30 p.m. and conclude at 10 p.m. The programme is as follows: 2 p.m., opening. 2.15 p.m., "Terminology and Ætiology of Skin Cancer", Dr. J. P. O'Brien and Dr. J. C. Belisario. 2.45 p.m., "Biochemical Investigations in Malignant Tumours of the Skin", Dr. G. Weber, Dr. V. J. McGovern and Dr. E. Kocsard. 3.15 p.m., "Skin Changes due to Solar Radiation", Dr. V. J. McGovern, Dr. G. Weber and Dr. W. Seymour Brooks. 4.15 p.m. "Clinical Types of Skin Cancer in Australia", Dr. W. H. Ward, Dr. W. W. Gunther and Dr. F. J. Collet. 4.45 p.m., "Keratoacanthoma", Dr. M. Havyatt, Dr. L. Cains and Dr. H. Sharp. 5.15 p.m., "Viral

Therapy of Skin Cancer", Dr. Y. Noguchi, Dr. E. Kocsard and Professor G. W. Milton. 7.30 p.m., "Radiation Therapy of Skin Cancer", Dr. V. W. Molesworth, Dr. H. J. Ham and Dr. M. B. Lewis. 8 p.m., "Surgical Therapy of Skin Cancer", Dr. F. W. Niesche, Professor G. W. Milton and Dr. E. W. Gibson. 8.30 p.m., "Chemotherapy of Skin Cancer", Dr. J. C. Belisario, Dr. K. W. Myers and Dr. L. G. Abbott. 9 p.m., "Diagnosis of Malignant Melanoblastoma", Dr. L. A. Musso, Dr. V. J. McGovern and Dr. J. P. O'Brien. 9.30 p.m., "Therapy of Malignant Melanoblastoma", Professor G. W. Milton, Dr. H. J. Ham and Dr. J. C. Belisario.

By arrangement with the New South Wales State Cancer Council, the symposium is open to all medical practitioners free of charge.

Special Courses in Advanced Medicine.

The Post-Graduate Committee in Medicine in the University of Sydney announces that a special course in advanced medicine suitable for candidates for the M.R.A.C.P. examination will begin on February 19, 1962. The course will be conducted daily from 9 a.m. to 5 p.m. for a period of five weeks, and will be held in conjunction with the Department of Medicine, University of Sydney. Further details will be announced at a later date. Early application should be made to the Course Secretary, The Post-Graduate Committee in Medicine, Herford House, 188 Oxford Street, Paddington. Telephone: 31 0671.

PRINCE HENRY HOSPITAL, SYDNEY, DEPARTMENT OF MEDICINE.

Seminar Programme, November, 1961.

SEMINARS are held at the Department of Medicine, Prince Henry Hospital, Sydney, on alternate Thursdays from 1.30 to 2.30 p.m., and are followed by case presentations. The location is the Nurses' Lecture Hall. The programme for November is as follows: November 2, "Treatment of Pulmonary Tuberculosis", Dr. T. Selby, Professor J. B. Johnston. November 16, "Management of Congestive Cardiac Failure", Dr. D. E. Anderson. November 30, "Vascular Surgery for Physicians", Professor G. D. Tracy.

THE MELBOURNE MEDICAL POST-GRADUATE COMMITTEE.

PROGRAMME FOR NOVEMBER, 1961.

Country Courses.

Camperdown.—On Saturday, November 4, at Camperdown Hospital, the following course will be given: 3.45 p.m., "The Management of Backache", Mr. John Jens; 5.15 p.m., "Recent Advances in Therapeutics", Dr. R. M. Biggins. The local secretary for this course is Dr. R. R. Sobey, 6 Spence Street, Warrnambool.

Traralgon.—On Saturday, November 11, at Traralgon and District Hospital, the following course will be given: 2.30 p.m., "Causes of Stillbirths and Neonatal Deaths", Professor Lance Townsend; 4 p.m., "The Premature Infant", Mr. J. Glyn White; 8 p.m., "Vaginal Discharge", Mr. J. K. Gabriel. Questions and discussions will follow each presentation. Dr. C. Bridges-Webb, 20 Kaye Street, Traralgon, is the local secretary.

Bendigo.—On Saturday, November 18, at Lister House Nursing School, Rowan Street, Bendigo, the following course will be given: 2.30 p.m., symposium on "Peptic Ulcer", Dr. Peter Parsons and Mr. James Guest; 4.30 p.m. "Intestinal Obstruction", Mr. C. W. Gale. Dr. I. D. B. Sutherland, 438 High Street, Golden Square, Bendigo, is the local secretary.

Ballarat.—On Thursday, November 23, at Ballarat Base Hospital, in the Board Room, at 8.15 p.m., Dr. Bryan Hudson will discuss "Recent Advances in the Management of Endocrine Conditions". Dr. I. C. Goy, 22 Ripon Street, Ballarat, is the local secretary.

Fees.—Fees for the above courses are at the rate of 15s. per lecture, but those who have paid an annual subscription to the Committee are invited without further charge.

Flinders Naval Depot.—On Wednesday, November 15, at Flinders Naval Depot, at 2.30 p.m., Professor R. R. H. Lovell will speak on "Blood Pressure". This lecture is given by arrangement with the Royal Australian Navy.

Overseas Visitor.

Mr. Lionel Cosin, F.R.C.S., Clinical Director of the Geriatric Unit, United Oxford Hospitals, United Kingdom, will be in Melbourne from November 5 to 15, visiting institutions and attending a geriatric conference. He will lecture for the Committee at 8.15 p.m. on Wednesday, November 8, in the Royal Society Hall, 8 LaTrobe Street, Melbourne, on "The Changing Relationships of Geriatrics and Internal Medicine". All members of the medical profession are invited to attend.

Summary of Courses to be Conducted in 1962.

A summary of courses to be conducted in Melbourne during 1962 will be published shortly.

Address.

The address of the Melbourne Medical Post-Graduate Committee is 394 Albert Street, East Melbourne. Telephone: FB 2547.

Obituary.

ALWYN LESLIE KINNA.

WE are indebted to DR. JOHN BROUGHTON for the following appreciation of the late Dr. Alwyn Kinna. A previous obituary notice appeared in the issue of August 5, 1961, at page 236.

The death of Alwyn Kinna has brought a sense of deep personal loss to very many families in the Hunter Valley. For more than twenty-five years his life was dedicated to bringing a little light into the dark recesses of the afflicted mind. Outside his own institution, many men and women, threatened with engulfment by real or imaginary forces, were helped to buttress the foundations of their daily lives. Perhaps only his intimates appreciated Kinna's full stature—the deep learning, kindness, humility and, above all, infinite wisdom; but many others also are saddened by his passing.

Notes and News.

The Frank G. Spurway Fellowship in the Rheumatic Diseases.

The Australian Rheumatism Council, because of a generous donation made to it in 1960 by Mr. Frank G. Spurway, is sponsoring the Frank G. Spurway Fellowship in the Rheumatic Diseases, tenable at the Royal North Shore Hospital of Sydney. Applications are invited from medical graduates for this fellowship. The successful applicant will be required to organize the Department of the Rheumatic Diseases under the direction of the honorary medical officers in charge, and he will be expected to perform research in this field under the supervision of the Director of the Institute of Medical Research of the hospital. Further details will be published in the advertisement columns of the Journal. Application forms and further information may be obtained from either of the following: Dr. W. Freeborn, General Medical Superintendent, Royal North Shore Hospital of Sydney, Crow's Nest, N.S.W.; A. F. Deer Esq., Honorary Secretary, Australian Rheumatism Council, P.O. Box 200, North Sydney, N.S.W.

Third International Conference on Alcohol and Road Traffic.

The third International Conference on Alcohol and Road Traffic will be held at B.M.A. House, Tavistock Square, London, from Monday to Friday, September 3 to 7, 1962. His Royal Highness the Duke of Edinburgh has graciously consented to be its Patron, and the President will be the British Minister of Transport. An International Committee and a Committee of Management have been appointed; Professor E. J. Wayne, Professor of the Practice of Medicine in the University of Glasgow, is Chairman of both Committees, and Dr. J. D. J. Havard, Assistant Secretary of the British Medical Association, is their Secretary. There will

be plenary sessions, sections and working parties. In the plenary sessions invited speakers will present papers covering the following topics: (i) law and law enforcement; (ii) pharmacological, physiological and psychological aspects, including analytical methods; (iii) the sociological aspects, including accident statistics, public information and insurance. The working parties will be composed of experts, and will discuss certain controversial points which have given rise to difficulty in practice. The sections will be devoted to short papers and discussions on them. The Committee of Management invites short papers on appropriate topics from intending participants; they should be submitted, typewritten, to the Secretary not later than December 31, 1961. Further information may be obtained from the Secretary at the address given above.

An Honour for Dr. K. W. Starr.

Dr. K. W. Starr has been elected to membership of the James IV Association of Surgeons. His sponsors were Sir Arthur Porritt and Sir Ralph Marnham.

Endorsement of British Standard 1583 Proposed.

The Standards Association of Australia announces for public critical review and comment a proposal to endorse the 1961 edition of the British Standard 1583 as a revised edition of the Australian Standard No. R.16 for one-mark pipettes. A minor amendment to suit Australian conditions is proposed. The 1961 edition incorporates fundamental changes in the use of pipettes, in that the drainage time (which used to be 15 seconds) is not included as part of the discharge time, so that the user now has to wait only for the meniscus to come to rest (nominally after three seconds) before withdrawing the receiver. Pipettes under the new standard will be marked with the letters "EX", indicating that they are calibrated to deliver the specified volume, whereas under earlier editions they were marked with the letter "D". This difference will also serve to distinguish pipettes manufactured to the new standard. These changes have been included in accordance with recommendations made by the International Organization for Standardization. The proposal to endorse British Standard 1583 is set out as Document 611, copies of which may be obtained from any office of the Standards Association. Copies of British Standard 1583 may be inspected or purchased at the headquarters of the Association, 157 Gloucester Street, Sydney, or at branch offices in the capital cities of all States and at Newcastle. Comment on Document 611 will be welcomed and should reach the Association before December 31, 1961.

Fulbright Travel Grants, 1962-1963.

The United States Educational Foundation announces that, under the provisions of the *Fulbright Act*, travel grants are available to Australian citizens to go the United States for study, research or lecturing at American universities and other institutions of higher learning during 1962-1963.

All candidates must fulfil the following requirements: (*a*) Candidates must hold a university degree or recognized professional qualifications. (*b*) Candidates must possess a guarantee of financial support in dollars for the proposed period of the visit to the United States. (*c*) Candidates must be affiliated with an approved American institution of higher learning. (*d*) The minimum period of study in the United States for students is one academic year. Lecturers must spend a minimum of one semester and research scholars three months in the United States (exclusive of travel time), of which about two-thirds should be spent at one university or recognized research institution. Grants cannot be given for attendance at conferences alone. All candidates are to return to reside permanently in Australia. (*e*) Candidates must be Australian citizens.

These travel grants are available for travel to the United States for or during the American academic year 1962-1963. All travel grants cover the cost of direct travel between the candidate's home in Australia and the institution he wishes to attend in the United States. No allowances are made for dependants' travel. All awards are made in open competition.

Applications are accepted in the following categories:

(*a*) Visiting lecturers and research scholars, senior category: for scholars who have achieved some professional standing at the post-doctoral level. The closing date for the receipt of applications is January 31, 1962.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 16, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	1(1)	3(3)	1	..	..	..	..	6
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	2	..	..	..	..	..	5	..	7
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	3(2)	16(15)	..	..	1	..	4	..	24
Diphtheria	1	..	..	..	..	..	..	..	1
Dysentery (Bacillary)	..	1(1)	..	4(4)	2(2)	..	2	..	9
Encephalitis	1	1(1)	..	..	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	1	..	..	1
Infective Hepatitis	101(43)	85(63)	17(6)	17(10)	3(3)	9(4)	2	9	243
Lead Poisoning	..	..	1(1)	..	..	..	..	..	1
Leprosy	..	..	..	..	..	..	3	..	3
Leptospirosis	..	..	1	..	..	..	..	..	1
Malaria	..	..	..	1(1)	..	1	..	..	2
Meningococcal Infection	1(1)	1	..	..	..	..	..	..	2
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	1	..	..	..	..	..	1
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	4(1)	1(1)	1	1(1)	1(1)	..	..	..	8
Puerperal Fever	2	..	..	..	..	..	..	..	2
Rubella	..	15(9)	..	4(3)	5(4)	..	..	..	24
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	8(3)	5(4)	1	3(1)	2(2)	..	1	20
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	1	..	..	..	..	..	..	1
Trachoma	..	..	..	..	1(1)	..	..	..	1
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	..	12(8)	11(9)	8(7)	4(2)	1	2	..	38
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

(b) Visiting lecturers and research scholars, junior category. In general, candidates should not be older than 30 years on the closing date set for the competition, but in exceptional cases, applications from older candidates will be considered. Applicants must have recently received a Ph.D. or anticipate completing the requirements for a Ph.D. prior to departing for the United States. The closing date for the receipt of applications is January 31, 1962.

(c) Post-graduate students: for graduates planning a regular course of study at a predoctoral level at an approved American university. The closing date for the receipt of applications is February 28, 1962.

(d) Special categories awards: for persons whose professions do not require highly specialized academic qualifications. These are open to visiting lecturers, research scholars and students. The closing date is March 31, 1962.

Candidates must lodge their applications by the closing dates, and applications postmarked after these dates will not be accepted.

Further information and application forms may be obtained from the United States Educational Foundation, P.O. Box 559, Canberra City, A.C.T.

Notice.

Reunion of 1952 N.S.W. Medical Graduates.

It is proposed to hold during 1962 a reunion of New South Wales medical graduates of 1952, provided that sufficient interest is displayed. Graduates are requested to write to "X.Y.Z.", c/- THE MEDICAL JOURNAL OF AUSTRALIA, indicating their interest in the matter. Further organization will be undertaken if there is sufficient response to this request.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Burke, Brian Vincent, M.B., B.S., 1955 (Univ. Queensland), D.P.M., Melbourne, 1960, Callan Park, Rozelle.

Cocking, Keith Josiah, M.B., B.S., 1959 (Univ. Sydney), c/- The Royal Newcastle Hospital, Newcastle.

Heppell, Robert Rutherford, M.B., B.S., 1960 (Univ. Sydney), Royal North Shore Hospital, St. Leonards, N.S.W.

Lee, Ang-Kim, M.B., B.S., 1959 (Univ. Sydney), The Boulevarde, Lakemba.

Quilty, William Joseph, M.B., B.S., 1959 (Univ. Sydney), The Women's Hospital, Crown Street, Sydney.

Toohey, John Joseph, M.B., B.S., 1960 (Univ. Sydney), St. Vincent's Hospital, Darlinghurst, N.S.W.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association:

Giorgio, Antonio, M.B., B.S., 1955 (Univ. Adelaide).

Hoopman, Peter William, M.B., B.S., 1958 (Univ. Adelaide).

Deaths.

THE following deaths have been announced:

SANGSTER.—William Clifford Sangster, on September 15, 1961, at Adelaide, S.A.

BROWN.—Kenneth Barnden Brown, on September 23, 1961, at Perth, W.A.

CARTER.—Harold Charles Ralph Carter, on October 4, 1961, at Melbourne, Victoria.

MCCREDIE.—Robert William McCredie, on October 4, 1961, at Sydney, N.S.W.

Diary for the Month.

OCTOBER 16.—Victorian Branch, B.M.A.: Finance Sub-Committee.
OCTOBER 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
OCTOBER 18.—Western Australian Branch, B.M.A.: General Meeting.
OCTOBER 19.—New South Wales Branch, B.M.A.: Clinical Meeting.
OCTOBER 19.—Victorian Branch, B.M.A.: Executive Meeting of Branch Council.
OCTOBER 20.—New South Wales Branch, B.M.A.: Ethics Committee.
OCTOBER 21.—Victorian Branch, B.M.A.: Country Branch Meeting (Bendigo).

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: 68-2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £6 *per annum* within Australia and the British Commonwealth of Nations, and £7 10s. *per annum* within America and foreign countries, payable in advance.